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FILE 'HOME' ENTERED AT 16:31:13 ON 30 JAN 2006

=> file .nash
=> s (angiotensin-converting enzyme or ACT) and crystal?
L1         2800 FILE MEDLINE
L2        18130 FILE CAPLUS
L3         9568 FILE SCISEARCH
L4          773 FILE LIFESCI
L5         2339 FILE BIOSIS
L6         2317 FILE EMBASE

TOTAL FOR ALL FILES
L7        35927 (ANGIOTENSIN-CONVERTING ENZYME OR ACT) AND CRYSTAL?

=> s l7 and x-ray
TOTAL FOR ALL FILES
L14        9391 L7 AND X-RAY

=> s l14 and (3-dimensional structure or crystal structure or 3-D structure)
TOTAL FOR ALL FILES
L21        5676 L14 AND (3-DIMENSIONAL STRUCTURE OR CRYSTAL STRUCTURE OR 3-D
                STRUCTURE)

=> s angiotensin-converting enzyme and crystal?
TOTAL FOR ALL FILES
L28         600 ANGIOTENSIN-CONVERTING ENZYME AND CRYSTAL?

=> s l28 and x-ray
TOTAL FOR ALL FILES
L35         187 L28 AND X-RAY

=> dup rem l35
PROCESSING COMPLETED FOR L35
L36          102 DUP REM L35 (85 DUPLICATES REMOVED)

=> s l35 not 2003-2006/py
TOTAL FOR ALL FILES
L43         133 L35 NOT 2003-2006/PY

=> dup rem l43
PROCESSING COMPLETED FOR L43
L44           76 DUP REM L43 (57 DUPLICATES REMOVED)

=> d ibib abs 1-76

L44  ANSWER 1 OF 76  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2002:676289  CAPLUS Full-text
DOCUMENT NUMBER:          137:211942
TITLE:                    Drug design against drug resistant mutants using
                          directed evolution and target protein conformation
                          changes
INVENTOR(S):              Stevens, Raymond C.; Orencia, Maria C.; Yoon, Jun
S.;
                          Hanson, Michael A.
PATENT ASSIGNEE(S):       The Scripps Research Institute, USA
SOURCE:                   PCT Int. Appl., 82 pp.
```

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002068933	A2	20020906	WO 2002-US6238	20020227
WO 2002068933	A3	20021121		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-272248P P 20010228

AB The present invention provides methods for identifying new drugs and potential inhibitors and modulators of drug-resistant variants of a target protein of a drug of interest. A drug-resistant variant according to the invention has at least one mutation resulting in a structural change, an activity change or a stability change as compared to the target protein. Such variants would include natural variants such as those encountered in the clinic, but preferably variants are selected by directed evolution methodol. The present invention relates to methods for designing new drugs useful against drug-resistant bacterial cells, viruses, mammalian cells and the like. The method involves identifying a target protein of the drug, selecting for drug-resistant variants that have an altered target protein (variant protein) by directed evolution, determining the three dimensional structure of the target and variant proteins and designing a new drug that can be effective against at least one drug-resistant variant. The present invention can be used to predict future mutations that lead to drug resistance and the type of drugs that are effective to combat such resistance.

L44 ANSWER 2 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:808426 CAPLUS Full-text
DOCUMENT NUMBER: 137:316076
TITLE: Preparation of lisinopril monohydrate
INVENTOR(S): Brown, John
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: U.S., 11 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6468976	B1	20021022	US 2001-950472	20010910

PRIORITY APPLN. INFO.: US 2001-950472 20010910

AB The present invention relates to a novel monohydrate form of 1-(N2-[(S)-1-carboxy-3-phenylpropyl]-L-lysyl)-L-proline known under the generic name lisinopril. Further, the present invention also relates to the use of the novel monohydrate form of lisinopril for the treatment of hypertension and other cardiovascular diseases, pharmaceutical compns. containing it as well as processes for the preparation of the monohydrate form of lisinopril. **Crystalline** lisinopril dihydrate was dissolved in 250 mL MeOH in a suitable vessel and heated briefly to reflux (60-65°). The solution was then filtered to remove any undissolved lisinopril and left to **crystallize** through self-cooling. The **crystals** formed were then isolated by filtration. The **crystalline** lisinopril dihydrate was dissolved in 50 mL water and then heated to about 45° until the volume of solvent (water) was reduced to about 10 mL. Isobutanol was then added and the resulting mixture was stirred overnight. The **crystals** formed were isolated by filtration and dried at 80° for 2 days. The monohydrate was characterized by **x- ray** diffraction and spectral methods.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L44 ANSWER 3 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:770146 CAPLUS Full-text
DOCUMENT NUMBER: 137:268487
TITLE: Amorphous lisinopril for treatment of hypertension and
cardiovascular diseases
INVENTOR(S): Roberts, Ronald John
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: U.S., 14 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6462174	B1	20021008	US 2001-891035	20010625
PRIORITY APPLN. INFO.:			US 2001-891035	20010625

AB The present invention relates to a novel form of lisinopril [(S)-1-[N2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline]. Further, the present invention also relates to the use of the novel amorphous form of lisinopril for the treatment of hypertension and other cardiovascular diseases, pharmaceutical compns. containing it as well as processes for the preparation of the amorphous form of lisinopril. **Crystalline** lisinopril dihydrate in a vial was placed in an oven at 120° for 2 h to remove water of **crystallization** Immediately on opening the oven, MeOH was added to the hot samples. The MeOH was evaporated down to 5 mL and the solution was allowed to cool to 25°. Sufficient acetone was added as an antisolvent to precipitate a white solid. This was filtered and dried in an oven at 60° for 1 h. The product was tested via HPLC to confirm that it was lisinopril. The lisinopril produced forms a surprisingly stable amorphous form which by **x-ray** powder diffraction gives a characteristic amorphous halo due to a lack of long range order, thus showing an absence of discernible diffraction peaks.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 4 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on
STN
ACCESSION NUMBER: 2002:951713 SCISEARCH Full-text
THE GENUINE ARTICLE: 617DC
TITLE: Sulfamide-based inhibitors for carboxypeptidase A. Novel type transition state analogue inhibitors for zinc proteases
AUTHOR: Park J D; Kim D H (Reprint); Kim S J; Woo J R; Ryu S E
CORPORATE SOURCE: Pohang Univ Sci & Technol, Ctr Integrated Mol Syst, Div Mol & Life Sci, Nam Ku, San 31 Hyoja Dong, Pohang 790784,
South Korea (Reprint); Pohang Univ Sci & Technol, Ctr Integrated Mol Syst, Div Mol & Life Sci, Nam Ku, Pohang 790784, South Korea; Korea Res Inst Biosci & Biotechnol, Ctr Cellular Switch Prot Struct, Yusong Gu, Taejon 305806,
South Korea
COUNTRY OF AUTHOR: South Korea
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (21 NOV 2002) Vol. 45, No.
24, pp. 5295-5302.
ISSN: 0022-2623.
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036
USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 63
ENTRY DATE: Entered STN: 13 Dec 2002
Last Updated on STN: 13 Dec 2002

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB N-Sulfamoylphenylalanine and its derivatives having varied alkyl groups on the terminal amino group were designed rationally as transition state analogue inhibitors for carboxypeptidase A (CPA) and synthesized. In CPA inhibitory assays the parent compound having the (S)configuration, i.e., (S)-1a, showed potent inhibitory activity with the K-i value of 0.64 muM. Its enantiomer was shown to be much less potent (K-i = 470 muM). Introduction of an alkyl group such as methyl or isopropyl group on the terminal amino group of (S)-1a lowered the inhibitory potency drastically. Introduction of a methyl group on the internal amino group of (S)-1a also caused a drastic reduction of the inhibitory activity. The structure of the CPA-(S)-1a complex determined by single-**crystal X- ray** diffraction reveals that the sulfamoyl moiety interacts with the zinc ion and functional groups at the active site of CPA, which is reminiscent of the postulated stabilization mode of a tetrahedral transition state in the CPA-catalyzed hydrolysis of a peptide substrate. On the basis of the design rationale and the binding mode of (S)-1a to CPA shown by **X-ray crystallographic** analysis, the present inhibitors are inferred to be a novel type of transition state analogue inhibitor for CPA.

L44 ANSWER 5 OF 76 MEDLINE on STN
ACCESSION NUMBER: 2002617470 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12207002
TITLE: **Crystal** structures of leukotriene A4 hydrolase in complex with captopril and two competitive tight-binding inhibitors.
AUTHOR: Thunnissen Marjolein M G M; Andersson Bjorn; Samuelsson Bengt; Wong Chi-Huey; Haeggstrom Jesper Z
CORPORATE SOURCE: Department of Biochemistry, University of Stockholm, Arrhenius Laboratories A4, S-106 91 Stockholm, Sweden.
SOURCE: FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2002 Oct) 16
(12) 1648-50. Electronic Publication: 2002-08-07.
Journal code: 8804484. ISSN: 1530-6860.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021011
Last Updated on STN: 20030105
Entered Medline: 20021217

AB Leukotriene (LT) A4 hydrolase/aminopeptidase is a bifunctional zinc enzyme that catalyzes the final step in the biosynthesis of LTB4, a potent chemoattractant and immune modulating lipid mediator. Here, we report a high-resolution **crystal** structure of LTA4 hydrolase in complex with captopril, a classical inhibitor of the zinc peptidase **angiotensin-converting enzyme**. Captopril makes few interactions with the protein, but its free thiol group is bound to the zinc, apparently accounting for most of its inhibitory action on LTA4 hydrolase. In addition, we have determined the structures of LTA4 hydrolase in complex with two selective tight-binding inhibitors, a thioamine and a hydroxamic acid. Their common benzyloxyphenyl tail, designed to mimic the carbon backbone of LTA4, binds into a narrow hydrophobic cavity in the protein. The free hydroxyl group of the hydroxamic acid makes a suboptimal, monodentate complex with the zinc, and strategies for improved inhibitor design can be deduced from the structure. Taken together, the three **crystal** structures provide the molecular basis for the divergent pharmacological profiles of LTA4 hydrolase inhibitors. Moreover, they help define the binding pocket for the fatty acid-derived epoxide LTA4 as well as the subsites for a tripeptide substrate, which in turn have important implications for the molecular mechanisms of enzyme catalyses.

L44 ANSWER 6 OF 76 MEDLINE on STN
ACCESSION NUMBER: 2002174815 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11906289
TITLE: Toward an optimal joint recognition of the S1' subsites of endothelin converting enzyme-1 (ECE-1), **angiotensin converting enzyme** (ACE), and neutral endopeptidase (NEP).
AUTHOR: Inguimbert Nicolas; Coric Pascale; Poras Herve; Meudal Herve; Teffot Franck; Fournie-Zaluski Marie-Claude;

Roques
Bernard P
CORPORATE SOURCE: Departement de Pharmacochimie Moleculaire et Structurale, INSERM U266, CNRS UMR 8600, UFR des Sciences Pharmaceutiques et biologiques, 4 Avenue de l'observatoire, 75270 Paris Cedex 06, France.
SOURCE: Journal of medicinal chemistry, (2002 Mar 28) 45 (7) 1477-86.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020322
Last Updated on STN: 20020430
Entered Medline: 20020429

AB The formation of vasoconstrictors (e.g., angiotensin II and endothelin) and the inactivation of vasodilators (e.g., bradykinin and atrial natriuretic) by membrane-bound zinc metallopeptidases are key mechanisms in the control of blood pressure and fluid homeostasis. The way in which these peptides modulate physiological functions has been intensively studied. With the aim to develop compounds that can jointly block the three metallopeptidases-neutral endopeptidase (NEP, neprilysin), **angiotensin-converting enzyme** (ACE), and endothelin-converting enzyme (ECE-1)-we studied the common structural specificity of the S1' subsites of these peptidases. Various mercaptoacyl amino acids of the general formula HS-CH2-CH(R1')CO-Trp-OH, possessing more or less constrained R1' side chains, were designed. The mercapto-acyl synthons contain one or two asymmetrical centers. The K(i) values of the separated stereoisomers of the most efficient inhibitors were used to determine the stereochemical preference of each enzyme. A guideline for the joint inhibition of the three peptidases was obtained with the (2R,3R) isomer of compound 13b. Its K(i) values on NEP, ACE, and ECE were 0.7, 43, and 26 nM, respectively.

L44 ANSWER 7 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:28687 CAPLUS Full-text
DOCUMENT NUMBER: 140:387693
TITLE: Synthesis and solution structure of the two peptides that represent the active-zinc containing-sites of **Angiotensin Converting Enzyme** (ACE)
AUTHOR(S): Galanis, Athanassios S.; Tzakos, Andreas G.; Spyroulias, Georgios A.; Troganis, Anastassios N.; Pairas, Goerge; Manessi-Zoupa, Evy; Gerothanassis, Ioannis P.; Cordopatis, Paul
CORPORATE SOURCE: Department of Pharmacy, University of Patras, Patras, GR-26504, Greece
SOURCE: Peptides 2002, Proceedings of the European Peptide Symposium, 27th, Sorrento, Italy, Aug. 31-Sept. 6, 2002 (2002), 802-803. Editor(s): Benedetti, Ettore; Pedone, Carlo. Edizioni Ziino: Castellammare di Stabia, Italy.

CODEN: 69EYXG; ISBN: 88-900948-1-8
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Two 36-peptides that represent the two catalytic centers of **angiotensin converting enzyme** (ACE) somatic isoform (ACEN-36 and ACEC-36 that correspond to H361-A396 and H959-A994 regions of ACE somatic isoform, resp.) were synthesized to obtain valuable insights for the structure of peptides through 1H NMR spectroscopy. Three-dimensional homol. models were generated using as template Thermolysin's **X-ray** structure in attempt to extract further structural information of the two ACE active sites. The two motifs HEMGH and EAIGD comprise the well-known gluzincins' zinc-binding motifs which are always found in all 3D **crystal** structures in helix conformation, the so-called "two active-site helixes". The NMR solution structure of the free ACEN-36 peptide, the 3D homol. ACE-Zn models and the TLN active site structure exhibit striking similarities.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 8 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on
STN
ACCESSION NUMBER: 2002:379389 SCISEARCH Full-text
THE GENUINE ARTICLE: 543GR
TITLE: Mechanism of action of zinc proteinases: A MNDO/d/H study
of alternative general-acid general-base catalytic pathways for carboxypeptidase-A
AUTHOR: Kilshtain-Vardi A; Shoham G; Goldblum A (Reprint)
CORPORATE SOURCE: Hebrew Univ Jerusalem, Sch Pharm, Dept Med Chem, IL-91120
Jerusalem, Israel (Reprint); Hebrew Univ Jerusalem, Sch Pharm, David R Bloom Ctr Pharm, IL-91120 Jerusalem, Israel; Hebrew Univ Jerusalem, Inst Chem, Dept Inorgan & Analyt Chem, IL-91120 Jerusalem, Israel
COUNTRY OF AUTHOR: Israel
SOURCE: INTERNATIONAL JOURNAL OF QUANTUM CHEMISTRY, (5 MAY 2002) Vol. 88, No. 1, pp. 87-98.
ISSN: 0020-7608.
PUBLISHER: JOHN WILEY & SONS INC, 111 RIVER ST, HOBOKEN, NJ 07030 USA
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 47
ENTRY DATE: Entered STN: 17 May 2002
Last Updated on STN: 17 May 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Two alternative pathways for peptide cleavage by water, both of the general-acid general-base type, have been followed by semiempirical theoretical calculations on a model of the active site. The system of 120 atoms has been carved out of high resolution **X-ray** coordinates of a carboxypeptidase A (CPA) complex with a ketomethylene inhibitor, pyroglutamic-N-Phe-(CH2CO)-Phe-OH. The method employed was a combination of MNDO/d and MNDO/H which,

together, enable one to deal with the effect of zinc and of multiple hydrogen bond interactions, respectively. The first step in both pathways is nucleophilic attack by a hydroxide on the peptide carbonyl, and the second is proton transfer to the nitrogen of the peptide. This second step presents the highest energy barrier for the reaction. Peptide bond cleavage is spontaneous subsequent to proton transfer. The two alternative paths differ little in barrier heights, but the thermodynamic enthalpy difference for the path of one mechanism is some 20 kcal/mol more stable than for the other, The first mechanism is the one proposed by Lipscomb (Acc Chem Res 1989, 22, 62-69) and the second, less stabilizing mechanism was proposed by Mock (J Biol Chem 1991, 266, 6369-6400). Under kinetic control, both reactions are feasible, and new experiments should be designed in order to clarify if only one of the two is operating under most of the relevant conditions. (C) 2002 Wiley Periodicals, Inc.

L44 ANSWER 9 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on
STN
ACCESSION NUMBER: 2002:810329 SCISEARCH Full-text
THE GENUINE ARTICLE: 599LJ
TITLE: The aminopeptidase from Aeromonas proteolytica: structure
and mechanism of co-catalytic metal centers involved in peptide hydrolysis
AUTHOR: Holz R C (Reprint)
CORPORATE SOURCE: Utah State Univ, Dept Chem & Biochem, Logan, UT 84322 USA
(Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: COORDINATION CHEMISTRY REVIEWS, (OCT 2002) Vol. 232, No. 1-2, pp. 5-26.
ISSN: 0010-8545.
PUBLISHER: ELSEVIER SCIENCE SA, PO BOX 564, 1001 LAUSANNE, SWITZERLAND.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 125
ENTRY DATE: Entered STN: 25 Oct 2002
Last Updated on STN: 25 Oct 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Enzymes containing multi-metal active sites are central to numerous biological processes and, consequently, characterization of their structure and function is a problem of outstanding importance. One of the least-explored groups of enzymes is the hydrolases that contain dinuclear metal centers. These enzymes play key roles in carcinogenesis, tissue repair, and protein degradation processes. In addition, some of these enzymes can catalyze the hydrolysis of phosphorus(V) compounds found in nerve gases and agricultural neurotoxins. The determination of detailed reaction mechanisms for these enzymes is required for the design of highly potent, specific inhibitors that can function as potential pharmaceuticals. Hydrolytic enzymes that contain dinuclear centers can use every first row divalent transition metal ion from manganese to zinc, except copper. In order to

understand the role of each metal ion in catalysis and the apparent non-selectivity of these enzymes towards divalent transition metal ions, it is critical that the reaction mechanism of a prototypical system be determined. The aminopeptidase from Aeromonas proteolytica (AAP) is one of the best mechanistically characterized hydrolytic enzymes that contains a dinuclear center and is, therefore, the focus of this review. (C) 2002 Elsevier Science B.V. All rights reserved.

L44 ANSWER 10 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:674624 CAPLUS Full-text
DOCUMENT NUMBER: 136:6325
TITLE: Asymmetric synthesis of BB-3497-A potent peptide deformylase inhibitor
AUTHOR(S): Pratt, L. M.; Beckett, R. P.; Davies, S. J.; Launchbury, S. B.; Miller, A.; Spavold, Z. M.; Todd, R. S.; Whittaker, M.
CORPORATE SOURCE: British Biotech Pharmaceuticals Limited, Cowley, Oxford, OX4 6LY, UK
SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), 11(19), 2585-2588
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:6325
AB By screening a library of metalloenzyme inhibitors, the N-formyl-hydroxylamine derivative BB-3497 was identified as a potent inhibitor of Escherichia coli peptide deformylase with antibacterial activity both in vitro and in vivo. The homochiral synthesis of BB-3497, involving a novel asym. Michael addition reaction is described.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 11 OF 76 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2001359978 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11227042
TITLE: Is there a future for renin inhibitors?.
AUTHOR: Fisher N D; Hollenberg N K
CORPORATE SOURCE: Departments of Radiology and Medicine, Brigham and Womens Hospital and Harvard Medical School, Boston, MA, USA.. nfisher@partners.org
SOURCE: Expert opinion on investigational drugs, (2001 Mar) 10 (3)
417-26. Ref: 33
Journal code: 9434197. ISSN: 1354-3784.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010827

Last Updated on STN: 20010827
Entered Medline: 20010823

AB Pharmacological interruption of the renin-angiotensin system is possible at three major sites, the **angiotensin-converting enzyme** (ACE), the AT1 receptor and at the interaction of renin with its substrate, angiotensinogen. Skeggs and his associates in 1957 argued logically but without prognostic accuracy that 'since renin is the initial and rate-limiting substance in the renin-angiotensin system, it would seem that the renin inhibition approach would be the most likely to succeed'. In fact, the development of agents that act at all three levels has enjoyed substantial success, yet renin inhibition, which showed early progress in studies in humans, has languished. Our task in this essay is to review the reasons for the slow evolution of renin inhibition and to discuss the potential of such agents in modern pharmacotherapy. All of the structure-action relationships have involved variation on the original peptide structure. The possibility that alternative approaches based on **x-ray crystallography** and reconstruction of the structure of the active site would lead to novel agents, appears not to have been explored systematically. This opportunity is all the more attractive because renin is one of the few targets that is actually soluble and amenable to **x-ray crystallographic** studies. At the moment, it appears that all renin inhibitor development programs have been closed, although hints periodically reappear to indicate that one company or another is pursuing a novel agent. The decision to close programs seems to have reflected not the therapeutic potential of renin inhibitors, but rather the cost of their synthesis, continuing problems with bioavailability and the remarkable success of the competitor class--the AngII antagonists. We believe that the potential of renin inhibition in human therapy has been under estimated and still shows substantial promise.

L44 ANSWER 12 OF 76 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2001370678 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11325479
TITLE: Chemical reactivity in solid-state pharmaceuticals: formulation implications.
AUTHOR: Byrn S R; Xu W; Newman A W
CORPORATE SOURCE: Purdue University, West Lafayette, IN 47907, USA.. sbyrn@pharmacy.purdue.edu
SOURCE: Advanced drug delivery reviews, (2001 May 16) 48 (1) 115-36. Ref: 46
Journal code: 8710523. ISSN: 0169-409X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010702
Last Updated on STN: 20010702
Entered Medline: 20010628

AB Solid-state reactions that occur in drug substances and formulations include solid-state phase transformations, dehydration/desolvation, and chemical reactions. Chemical reactivity is the focus of this chapter. Of particular interest are cases where the drug-substance may be unstable or react with excipients in the formulation. Water absorption

can enhance molecular mobility of solids and lead to solid-state reactivity. Mobility can be measured using various methods including glass transition (T(g)) measurements, solid-state NMR, and **X-ray crystallography.** Solid-state reactions of drug substances can include oxidation, cyclization, hydrolysis, and deamidation. Oxidation studies of vitamin A, peptides (DL-Ala-DL-Met, N-formyl-Met-Leu-Phe methyl ester, and Met-enkaphalin acetate salt), and steroids (hydrocortisone and prednisolone derivatives) are discussed. Cyclization reactions of **crystalline** and amorphous **angiotensin-converting enzyme** (ACE) inhibitors (spirapril hydrochloride, quinapril hydrochloride, and moexipril) are presented which investigate mobility and chemical reactivity. Examples of drug-excipient interactions, such as transacylation, the Maillard browning reaction, and acid base reactions are discussed for a variety of compounds including aspirin, fluoxitine, and ibuprofen. Once solid-state reactions are understood in a pharmaceutical system, the necessary steps can be taken to prevent reactivity and improve the stability of drug substances and products.

L44 ANSWER 13 OF 76 MEDLINE on STN
ACCESSION NUMBER: 2001082939 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11015691
TITLE: Structural characterization of three **crystalline** modifications of telmisartan by single **crystal** and high-resolution **X-ray** powder diffraction.
AUTHOR: Dinnebier R E; Sieger P; Nar H; Shankland K; David W I
CORPORATE SOURCE: Laboratory of Crystallography, University of Bayreuth, D-95440, Bayreuth, Germany..
robert.dinnebier@unibayreuth.de
SOURCE: Journal of pharmaceutical sciences, (2000 Nov) 89 (11) 1465-79.
Journal code: 2985195R. ISSN: 0022-3549.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010105

AB Three **crystalline** modifications (A, B, and C) of 4'-[[2-n-propyl-4-methyl-6-(1-methyl-benzimidazol-2-yl)benzi midazol-1-yl]methyl]biphenyl-2-carboxylic acid (INN name, telmisartan) have been detected and their **crystal** structures have been determined by single-**crystal X-ray** diffraction (pseudopolymorph C) and the method of simulated annealing from high-resolution **X-ray** powder diffraction data (polymorphs A and B). The compound is of interest because of its use as an angiotensin II receptor antagonist. Polymorph A **crystallizes** in space group P2(I)/c, Z = 4, with unit cell parameters a = 18.7798(3), b = 18.1043(2), and c = 8.00578(7) A, beta = 97.066(1) degrees, and V = 2701.31 A(3). Polymorph B **crystallizes** in space group P2(I)/a, Z = 4, with unit cell parameters a = 16.0646(5), b = 13.0909(3), and c = 13.3231(3) A, beta = 99.402(1) degrees, and V = 2764.2(1) A(3). The solvated form C **crystallizes** in space group C2/c, Z = 8, with unit cell parameters a = 30.990(5), b = 13.130(3), and c = 16.381(3) A, beta = 95.02(2) degrees, and V = 6639(2)

A(3). For the structure solutions of polymorphs A and B, 13 degrees of freedom (3 translational, 3 orientational, 7 torsion angles) were determined in approximately 2 h of computer time, demonstrating that the **crystal** packing and the molecular conformation of medium-sized (MW approximately 500) pharmaceutical compounds can now be solved quickly and routinely from high-resolution **X-ray** powder diffraction data. Copyright 2000 Wiley-Liss, Inc.

L44 ANSWER 14 OF 76 MEDLINE on STN

ACCESSION NUMBER: 2000418692 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10903938
TITLE: Structure-based drug design: the discovery of novel nonpeptide orally active inhibitors of human renin.
AUTHOR: Rahuel J; Rasetti V; Maibaum J; Rueger H; Goschke R; Cohen N C; Stutz S; Cumin F; Fuhrer W; Wood J M; Grutter M G
CORPORATE SOURCE: Core Technology Area, Novartis Pharma AG, Metabolic and Cardiovascular Diseases, Basle, Switzerland.
SOURCE: Chemistry & biology, (2000 Jul) 7 (7) 493-504. Journal code: 9500160. ISSN: 1074-5521.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915
Last Updated on STN: 20000915
Entered Medline: 20000906

AB BACKGROUND: The aspartic proteinase renin plays an important physiological role in the regulation of blood pressure. It catalyses the first step in the conversion of angiotensinogen to the hormone angiotensin II. In the past, potent peptide inhibitors of renin have been developed, but none of these compounds has made it to the end of clinical trials. Our primary aim was to develop novel nonpeptide inhibitors. Based on the available structural information concerning renin-substrate interactions, we synthesized inhibitors in which the peptide portion was replaced by lipophilic moieties that interact with the large hydrophobic S1/S3-binding pocket in renin. RESULTS: **Crystal** structure analysis of renin-inhibitor complexes combined with computational methods were employed in the medicinal-chemistry optimisation process. Structure analysis revealed that the newly designed inhibitors bind as predicted to the S1/S3 pocket. In addition, however, these compounds interact with a hitherto unrecognised large, distinct, sub-pocket of the enzyme that extends from the S3-binding site towards the hydrophobic core of the enzyme. Binding to this S3(sp) sub-pocket was essential for high binding affinity. This unprecedented binding mode guided the drug-design process in which the mostly hydrophobic interactions within subsite S3(sp) were optimised. CONCLUSIONS: Our design approach led to compounds with high in vitro affinity and specificity for renin, favourable bioavailability and excellent oral efficacy in lowering blood pressure in primates. These renin inhibitors are therefore potential therapeutic agents for the treatment of hypertension and related cardiovascular diseases.

L44 ANSWER 15 OF 76 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2000187354 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10720645
TITLE: Antiangiogenic effects of S-nitrosocaptopril **crystals** as a nitric oxide donor.
AUTHOR: Jia L; Wu C C; Guo W; Young X
CORPORATE SOURCE: La Jolla Pharmaceuticals, 11283 Carmel Creek Rd., San Diego, CA 92130, USA.. lgia@access1.net
SOURCE: European journal of pharmacology, (2000 Mar 10) 391 (1-2) 137-44.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000511

AB Angiogenesis is the formation of new capillaries from preexisting vessels by migration and proliferation of endothelial cells, which produce a cellular signaling messenger, nitric oxide (NO). The purpose of the present study was to examine the effects of exogenous NO donors on angiogenesis by using a novel **crystalline** NO donor, S-nitrosocaptopril. The characteristic **X-ray** diffraction pattern of S-nitrosocaptopril was demonstrated for the first time. On primary capillary endothelial cells pretreated with vascular endothelium growth factor (VEGF), S-nitrosocaptopril (1-500 microM), but not captopril, produced a dose-dependent inhibition of endothelial proliferation. On chick embryos of entire living eggs, gelatin sponges adsorbed with VEGF were implanted on the embryo chorioallantoic membrane to promote vascular growth activity within the sponges. Addition of S-nitrosocaptopril **crystals** (0.1 mg) to the gelatin sponges markedly reduced vascular density around the sponges, whereas captopril did not inhibit neovascularization. The vascular hemoglobin content surrounding each of the gelatin sponges was determined as a confirmatory test. S-nitrosocaptopril, but not captopril, significantly decreased the hemoglobin content of the embryo tissues immediately surrounding the gelatin sponges. In conclusion, S-nitrosocaptopril exerts an inhibitory effect on angiogenesis. This newly discovered function of S-nitrosocaptopril appears to be governed by distinct structural NO moiety.

L44 ANSWER 16 OF 76 MEDLINE on STN
ACCESSION NUMBER: 2000130393 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10664545
TITLE: Physical characteristics and chemical degradation of amorphous quinapril hydrochloride.
AUTHOR: Guo Y; Byrn S R; Zografi G
CORPORATE SOURCE: School of Pharmacy, University of Wisconsin-Madison, Madison, WI 53706, USA.
SOURCE: Journal of pharmaceutical sciences, (2000 Jan) 89 (1) 128-43.
Journal code: 2985195R. ISSN: 0022-3549.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000407

AB This study was designed to investigate the relationships between the solid-state chemical instability and physical characteristics of a model drug, quinapril hydrochloride (QHCl), in the amorphous state. Amorphous QHCl samples were prepared by rapid evaporation from dichloromethane solution and by grinding and subsequent heating of the **crystalline** form. Physical characteristics, including the glass transition temperature and molecular mobility, were determined using differential scanning calorimetry, thermogravimetric analysis, powder **x- ray** diffractometry, polarizing microscopy, scanning electron microscopy, and infrared spectroscopy. The amorphous form of QHCl, produced by both methods, has a T(g) of 91 degrees C. Isothermal degradation studies showed that cyclization of QHCl occurred at the same rate for amorphous samples prepared by the two methods. The activation energy was determined to be 30 to 35 kcal/mol. The rate of the reaction was shown to be affected by sample weight, dilution through mixing with another solid, and by altering the pressure above the sample. The temperature dependence for chemical reactivity below T(g) correlated very closely with the temperature dependence of molecular mobility. Above T(g), however, the reaction was considerably slower than predicted from molecular mobility. From an analysis of all data, it appears that agglomeration and sintering of particles caused by softening of the solid, particularly above T(g), and a resulting reduction of the particle surface/volume ratio play a major role in affecting the reaction rate by decreasing the rate of removal of the gaseous HCl product. Copyright 2000 Wiley-Liss, Inc. and the American Pharmaceutical Association J Pharm Sci 89: 128-143, 2000

L44 ANSWER 17 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:796019 CAPLUS Full-text
TITLE: Metallated **angiotensin converting enzyme** inhibitors: Synthesis and biological applications.
AUTHOR(S): Pandurangi, Raghu S.
CORPORATE SOURCE: Chemistry Department, University of Missouri, Columbia, MO, 65211, USA
SOURCE: Abstracts of Papers, 220th ACS National Meeting, Washington, DC, United States, August 20-24, 2000 (2000) MEDI-022
CODEN: 69FZC3
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; Meeting Abstract
LANGUAGE: English

AB De novo generation of **Angiotensin Converting Enzyme** (ACE) has been implicated in the development of tissue fibrosis following myocardial infarction (MI). High d. localization of ACE in infarcted heart and its relationship to tissue repair lead to the development of ACE inhibitors to suppress ACE in vivo. Lisinopril is a clin. approved drug for controlling hypertension and congestive heart failure. Modification of lisinopril by bifunctional chelating agents (BFCAs) carrying diagnostic radiomarker (e.g. 99mTc) combines high target potential of ACE inhibitors and high noninvasive imaging potential of the radiometal.

Synthesis of metalated ACE inhibitors (with rhenium as a surrogate to technetium) poses a challenge to the conformational and biol. activity of native lisinopril. Here, we present a novel synthetic protocol for functionalization of lisinopril by peptidomimitic chelating framework with retention of the inhibitory potency data, followed by the characterization by multinuclide NMR and single **crystal X-Ray.**

L44 ANSWER 18 OF 76 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:447717 BIOSIS Full-text
DOCUMENT NUMBER: PREV200000447717
TITLE: Metallated **Angiotensin Converting Enzyme** inhibitors: Synthesis and biological applications.
AUTHOR(S): Pandurangi, Raghu S. [Reprint author]
CORPORATE SOURCE: Chemistry Department, University of Missouri, 601S, College Ave, Columbia, MO, 65211, USA
SOURCE: Abstracts of Papers American Chemical Society, (2000) Vol. 220, No. Part 1, pp. MEDI 22. print.
Meeting Info.: 220th National Meeting of the American Chemical Society. Washington DC, Washington DC, USA. August 20-24, 2000. American Chemical Society.
CODEN: ACSRAL. ISSN: 0065-7727.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Oct 2000
Last Updated on STN: 10 Jan 2002

L44 ANSWER 19 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:441255 SCISEARCH Full-text
THE GENUINE ARTICLE: 202TQ
TITLE: Zinc coordination and substrate catalysis within the neuropeptide processing enzyme endopeptidase EC 3.4.24.15 - Identification of active site histidine and glutamate residues
AUTHOR: Cummins P M; Pabon A; Margulies E H; Glucksman M J (Reprint)
CORPORATE SOURCE: CUNY Mt Sinai Sch Med, Fishberg Res Ctr Neurobiol, Box 1065, 1425 Madison Ave, New York, NY 10029 USA (Reprint); CUNY Mt Sinai Sch Med, Fishberg Res Ctr Neurobiol, New York, NY 10029 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (4 JUN 1999) Vol. 274, No. 23, pp. 16003-16009.
ISSN: 0021-9258.
PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
DOCUMENT TYPE: Article; Journal

LANGUAGE: English
REFERENCE COUNT: 62
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Endopeptidase EC 5.4.24.15 (EP24.15) is a zinc metalloendopeptidase that is broadly distributed within the brain, pituitary, and gonads. Its substrate specificity includes a number of physiologically important neuropeptides such as neurotensin, bradykinin, and gonadotropin-releasing hormone, the principal regulatory peptide for reproduction. In studying the structure and function of EP24.15, we have employed in. vitro mutagenesis and subsequent protein expression to genetically dissect the enzyme and allow us to glean insight into the mechanism of substrate binding and catalysis, Comparison of the sequence of EP24.15 with bacterial homologues previously solved by **x-ray crystallography** and used as models for mammalian metalloendopeptidases, indicates conserved residues. The active site of EP24.15 exhibits an HEXXH motif, a common feature of zinc metalloenzymes, Mutations have confirmed the importance, for binding and catalysis, of the residues (His(473), Glu(474), and His(477)) within this motif, A third putative metal ligand, presumed to coordinate directly to the active site zinc ion in concert with His(473) and His(477), has been identified as Glu(502). Conservative alterations to these residues drastically reduces enzymatic activity against both a putative physiological substrate and a synthetic quenched fluorescent substrate as well as binding of the specific active site-directed inhibitor, N-[1-(RS) -carboxy-3- phenylpropyl] -Ala-Ala-Tyr-p-aminobenzoate, the binding of which we have shown to be dependent upon the presence, and possibly coordination, of the active site zinc ion. These studies contribute to a more complete understanding of the catalytic mechanism of EP24.15 and will aid in rational design of inhibitors and pharmacological agents for this class of enzymes.

L44 ANSWER 20 OF 76 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 1999435729 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10504225
TITLE: **Crystal** structures of alpha-mercaptoacyldipeptides in the thermolysin active site: structural parameters for a Zn monodentation or bidentation in metalloendopeptidases.
AUTHOR: Gaucher J F; Selkti M; Tiraboschi G; Prange T; Roques B P; Tomas A; Fournie-Zaluski M C
CORPORATE SOURCE: Laboratoire de Cristallographie & RMN Biologiques, CNRS EP 2075, UFR des Sciences Pharmaceutiques et Biologiques, 4 Avenue de l'Observatoire, 75270 Paris Cedex 06, France.
SOURCE: Biochemistry, (1999 Sep 28) 38 (39) 12569-76.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101
Last Updated on STN: 20000303
Entered Medline: 19991020

AB Three alpha-mercaptoacyldipeptides differing essentially in the size of their C-terminal residues have been **crystallized** in the thermolysin active site. A new mode of binding was observed for 3 [HS-CH(CH(2)Ph)CO-Phe-Tyr] and 4 [HS-CH((CH(2))(4)CH(3))CO-Phe-Ala], in which the mercaptoacyl moieties act as bidentates with Zn-S and Zn-O distances of 2.3 and 2.4 A, respectively, the side chains fitting the S(1), S(1)', and S(2)' pockets. Moreover, a distance of 3.1 A between the sulfur atom and the OE1 of Glu(143) suggests that they are H-bonded and that one of these atoms is protonated. This H-bond network involving Glu(143), the mercaptoacyl group of the inhibitor, and the Zn ion could be considered a "modified" transition state mimic of the peptide bond hydrolysis. Due to the presence of the hindering (5-phenyl)proline, the inhibitor HS-CH(CH(2)Ph)CO-Gly-(5-Ph)Pro (2) interacts through the usual Zn monodentation via the thiol group and occupancy of S(1)' and S(2)' subsites by the aromatic moieties, the proline ring being outside the active site. The inhibitory potencies are consistent with these structural data, with higher affinities for 3 (4.2 x 10(-)(8) M) and 4 (4.8 x 10(-)(8) M) than for 2 (1.2 x 10(-)(6) M). The extension of the results, obtained with thermolysin being considered as the model of physiological zinc metallopeptidases, allows inhibitor-recognition modes for other peptidases, such as **angiotensin converting enzyme** and neutral endopeptidase, to be proposed and opens interesting possibilities for the design of new classes of inhibitors.

L44 ANSWER 21 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:629363 SCISEARCH Full-text
THE GENUINE ARTICLE: 228LG
TITLE: 2-benzyl-2-methylsuccinic acid as inhibitor for carboxypeptidase A. Synthesis and evaluation
AUTHOR: Lee M; Jin Y; Kim D H (Reprint)
CORPORATE SOURCE: Pohang Univ Sci & Technol, Ctr Biofunct Mol, San 31 Hyoja Dong, Pohang 790784, South Korea (Reprint); Pohang Univ Sci & Technol, Ctr Biofunct Mol, Pohang 790784, South Korea; Pohang Univ Sci & Technol, Dept Chem, Pohang 790784, South Korea
COUNTRY OF AUTHOR: South Korea
SOURCE: BIOORGANIC & MEDICINAL CHEMISTRY, (AUG 1999) Vol. 7, No. 8, pp. 1755-1760.
ISSN: 0968-0896.
PUBLISHER: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 19
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Recently, Asante-Appiah et al. (Asante-Appiah, E.; Seetharaman, J.; Sicheri, F.; Yang, D. S.-C.; Chan, W. W.-C. Biochemistry

1997, 36, 8710-8715) reported that 2-ethyl-2-methylsuccinic acid isa highly potent inhibitor for carboxypeptidase A (CPA), a prototypic zinc protease. The **X-ray crystal** structure of the complex of the enzyme formed with 2-ethyl-2-methylsuccinic acid revealed that at the active site of CPA there is present a small cavity which accommodates the methyl group of the inhibitor. These investigators postulated that incorporation of a methyl group at the alpha-position to the carboxylate of existing inhibitors of CPA would improve the inhibitory potency. We have synthesized racemic and optically active 2-benzyl-2-methylsuccinic acids and evaluated their inhibitory activities for CPA to find the K-i values to be 0.28, 0.15, and 17 mu M for racemic form, (R)-, and (S)-enantiomer, respectively. Contrary to the expectation, the effect on the binding affinity by the incorporation of the methyl group is minimal. The validity of the proposition that the small cavity may be utilized for the improvement of the inhibitory potency appears questionable. (C) 1999 Elsevier Science Ltd. All rights reserved.

L44 ANSWER 22 OF 76 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 1999134396 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9931257
TITLE: The 2.2 A **crystal** structure of human chymase in complex with succinyl-Ala-Ala-Pro-Phe-chloromethylketone: structural explanation for its dipeptidyl carboxypeptidase specificity.
AUTHOR: Pereira P J; Wang Z M; Rubin H; Huber R; Bode W; Schechter N M; Strobl S
CORPORATE SOURCE: Abteilung fur Strukturforschung, Max-Planck-Institut fur Biochemie, Am Klopferspitz 18a, Martinsried, D-82152, Germany.
CONTRACT NUMBER: AR42931 (NIAMS)
HL50523 (NHLBI)
SOURCE: Journal of molecular biology, (1999 Feb 12) 286 (1) 163-73.
Journal code: 2985088R. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1PJP
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990413
Last Updated on STN: 20000303
Entered Medline: 19990329

AB Human chymase (HC) is a chymotrypsin-like serine proteinase expressed by mast cells. The 2.2 A **crystal** structure of HC complexed to the peptidyl inhibitor, succinyl-Ala-Ala-Pro-Phe-chloromethylketone (CMK), was solved and refined to a **crystallographic** R-factor of 18.4 %. The HC structure exhibits the typical folding pattern of a chymotrypsin-like serine proteinase, and shows particularly similarity to rat chymase 2 (rat mast cell proteinase II) and human cathepsin G. The peptidyl-CMK inhibitor is covalently bound to the active-site residues Ser195 and His57; the peptidyl moiety juxtaposes the S1 entrance frame segment 214-217 by

forming a short antiparallel beta-sheet. HC is a highly efficient **angiotensin-converting enzyme** . Modeling of the chymase-angiotensin I interaction guided by the geometry of the bound chloromethylketone inhibitor indicates that the extended substrate binding site contains features that may generate the dipeptidyl carboxypeptidase-like activity needed for efficient cleavage and activation of the hormone. The C-terminal carboxylate group of angiotensin I docked into the active-site cleft, with the last two residues extending beyond the active site, is perfectly localized to make a favorable hydrogen bond and salt bridge with the amide nitrogen of the Lys40-Phe41 peptide bond and with the epsilon-ammonium group of the Lys40 side-chain. This amide positioning is unique to the chymase-related proteinases, and only chymases from primates possess a Lys residue at position 40. Thus, the structure conveniently explains the preferred conversion of angiotensin I to angiotensin II by human chymase. Copyright 1999 Academic Press.

L44 ANSWER 23 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 1998:676010 CAPLUS Full-text
DOCUMENT NUMBER: 130:9978
TITLE: Retention of Inhibitory Potency of an ACE Inhibitor Conjugated with Rh(III) and Pd(II) (Iminophosphorano)phosphines. Synthesis and **X -ray** Structural Investigations
AUTHOR(S): Pandurangi, Raghoottama S.; Katti, Kattesh V.; Stillwell, Loreen; Barnes, Charles L.
CORPORATE SOURCE: Department of Internal Medicine, University of Missouri, Columbia, MO, 65211, USA
SOURCE: Journal of the American Chemical Society (1998), 120(44), 11364-11373
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Succinimido, amido, and ester functionalized tetrafluoroaryl azides selectively oxidize bisdiphenylphosphinomethane at one of the P(III) centers giving (iminophosphorano)phosphines 6, 7, and 8 resp. in high yields. Succinimido functionalized perfluoroaryl azido (iminophosphorano)phosphine is attached to **angiotensin converting enzyme** (ACE) inhibitor, lisinopril at one end, leaving the other end for chelation to Rh(III) and Pd(II) precursors including radioactive analogs establishing the hetero-bifunctionality for potential in vivo tracking of the radiotracer. The measurement of inhibitory potency of lisinopril-metal conjugates (Rh and Pd), modified through the primary amine reveals an increase in inhibitory potency, although small, retaining the target potential of native lisinopril toward specific biol. sites. However, direct complexation using the carboxylic groups of lisinopril with a Cu precursor resulted in the reduction of inhibitory potency from nM to μM levels rendering it less useful for applications as an ACE inhibitor. Single-**crystal x- ray** structural study of the Rh(III) perfluoroaryl (iminophosphorano)phosphine complex 12 shows a distorted mer octahedral configuration with two ligands per metal center and only one of the phosphiniminato N atom coordinating to the metal. Pd(II) complex 18 reveals that the metal is bound to the iminato N atom and the P(III) center via cis disposition to form a five-membered ring. **X- ray** data for 12.MeCN: triclinic, P.hivin.1, a

11.570(6) Å b 13.668 Å(7) c 20.709(10) Å, α 86.068(10), β 83.774(10), γ 83.503(10)°V = 3229.6(3) Å3, Z = 2, R = 0.028, Rw = 0.050. **X-ray** data for 18.MeCN: triclinic, P.hivin.1, a 11.457(3) Å, b 12.223(3) Å, c 13.219(4) Å, α 89.98(20), β 73.710(20), γ 69.980(20)°, V = 1665.7(8) Å3, Z = 2, R = 0.024, Rw = 0.031.

REFERENCE COUNT: 102 THERE ARE 102 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 24 OF 76 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1998134838 EMBASE Full-text
TITLE: Synthesis of the **angiotensin-converting enzyme** inhibitor (±)-A58365A.
AUTHOR: Clive D.L.J.; Coltart D.M.
CORPORATE SOURCE: D.L.J. Clive, Chemistry Department, University of Alberta,
Edmonton, Alta. T6G 2G2, Canada
SOURCE: Tetrahedron Letters, (23 Apr 1998) Vol. 39, No. 17, pp. 2519-2522. .
Refs: 15
ISSN: 0040-4039 CODEN: TELEAY
PUBLISHER IDENT.: S 0040-4039(98)00384-0
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19980618
Last Updated on STN: 19980618

AB **Crystalline** (±)-A58365A (1), an inhibitor of **angiotensin-converting enzyme**, was synthesized by a process based on enyne radical cyclization (13a,b → 14a,b). The starting material for this process was constructed by coupling the spiro lactone 6 with the amino acid 7, followed by elaboration into 13a,b.

L44 ANSWER 25 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1998:764964 SCISEARCH Full-text
THE GENUINE ARTICLE: 126BV
TITLE: Design of mechanism-based carboxypeptidase a inactivators
on the basis of the **X-ray** **crystal** structure and catalytic reaction pathway
AUTHOR: Lee K J; Kim D H (Reprint)
CORPORATE SOURCE: Pohang Univ Sci & Technol, Dept Chem, San 31 Hyojadong, Pohang 790784, South Korea (Reprint); Pohang Univ Sci & Technol, Dept Chem, Pohang 790784, South Korea; Pohang Univ Sci & Technol, Ctr Biofunct Mol, Pohang 790784, South
Korea
COUNTRY OF AUTHOR: South Korea
SOURCE: BIOORGANIC & MEDICINAL CHEMISTRY, (SEP 1998) Vol. 6, No.

9, pp. 1613-1622.
ISSN: 0968-0896.
PUBLISHER: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 52
ENTRY DATE: Entered STN: 1998
Last Updated on STN: 1998
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The **X-ray crystal** structure of the complex of carboxypeptidase A (CPA) and Gly-Tyr, has been documented. The **crystal** structure reveals that both the amide carbonyl oxygen and the terminal amino nitrogen of Gly-Tyr coordinate to the active site zinc ion of CPA in a bidentate fashion, whereby the zinc-bound water molecule is displaced by the amino group. As to the catalytic mechanism of CPA, it is generally believed that while in the cases of ester substrates the carboxylate of Glu-270 functions as the nucleophile which attacks the scissile carbonyl carbon (anhydride pathway), in the case of peptide substrates the zinc-bound water molecule attacks the scissile peptide bond (general base pathway). In light of the **X-ray crystal** structure and the proposed catalytic mechanism for the enzyme, it is envisioned that the ester bond of O-(hydroxyacetyl)-L-beta- phenyllactic acid (L-1) would be hydrolyzed by the attack of the carboxylate of Glu-270 to generate an anhydride intermediate. The latter intermediate would then undergo an intramolecular rearrangement initiated by the attack of the hydroxyl to result in to form an ester bond with the Glu-270 carboxylate. This ester formation impairs the catalytic activity of CPA. We have demonstrated using kinetic analysis that L-1 is indeed an inactivator for the enzyme having the k(inact)/K-I value of 0.057 M-1 s(-1). We have also demonstrated that N-(hydroxyacetyl)-L-phenylalanine (L-2) inactivates the enzyme with the k(inact)/K-I value of 0.071 M-1 s(-1), suggesting that the carboxylate becomes to attack the peptide carbonyl carbon to generate the same anhydride intermediate as that formed in the inactivation of CPA by L-1. The formation of the anhydride intermediate rather than a tetrahedral transition state that is expected for peptide type substrates was envisioned to occur on the ground that the zinc-bound water molecule is displaced by the hydroxyl of L-2 upon binding to the enzyme. (C) 1998 Elsevier Science Ltd. All rights reserved.

L44 ANSWER 26 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 1998:378359 CAPLUS Full-text
DOCUMENT NUMBER: 129:136480
TITLE: Structural characterization and solution rotational isomerism of delapril hydrochloride, a dipeptide **angiotensin-converting enzyme** inhibitor
AUTHOR(S): Redenti, Enrico; Zanol, Margherita; Amari, Gabriele; Ventura, Paolo; Fronza, Giovanni; Bacchi, Alessia; Pelizzi, Giancarlo
CORPORATE SOURCE: Chemical and Biopharmaceutical Department, Chiesi Farmaceutici SpA, Parma, 43100, Italy
SOURCE: Farmaco (1998), 53(3), 214-223

CODEN: FRMCE8; ISSN: 0014-827X
PUBLISHER: Elsevier Science S.A.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The solid state structure of delapril hydrochloride was determined by single- **crystal x-ray** diffraction anal. The comparison between delapril and other **angiotensin- converting enzyme** (ACE) inhibitors of the same family is discussed with regard to the geometry of the phenomenol. active site of the enzyme. In the solid state the amide bond conformation resulted in being trans, whereas, in solution, NMR spectra indicate that the mol. exists as a mixture of rotational isomers trans and cis (approx. 70:30). The free energy of activation for the hindered rotation about the amide bond was determined by line-shape anal. The attempt to isolate possible conformational polymorphs failed, indicating that the trans conformation is favored when mols. pack together in the **crystal.**
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L44 ANSWER 27 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on
STN
ACCESSION NUMBER: 1998:263373 SCISEARCH Full-text
THE GENUINE ARTICLE: ZE824
TITLE: Modeling of inhibitor-metalloenzyme interactions and selectivity using molecular mechanics grounded in quantum
chemistry
AUTHOR: Garmer D R; Gresh N (Reprint); Roques B P
CORPORATE SOURCE: UFR Sci Pharmaceut & Biol, USA Dept Pharmacochim Mol & Struct, URA D1500 CNRS, U266 INSERM, 4 Ave Observ, F-75270
Paris 06, France (Reprint); UFR Sci Pharmaceut & Biol, USA
Dept Pharmacochim Mol & Struct, URA D1500 CNRS, U266 INSERM, F-75270 Paris 06, France; Mt Sinai Sch Med, Dept Physiol & Biophys, New York, NY USA
COUNTRY OF AUTHOR: France; USA
SOURCE: PROTEINS-STRUCTURE FUNCTION AND GENETICS, (1 APR 1998) Vol. 31, No. 1, pp. 42-60.
ISSN: 0887-3585.
PUBLISHER: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW
YORK, NY 10158-0012 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 65
ENTRY DATE: Entered STN: 1998
Last Updated on STN: 1998
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB We investigated the binding properties of the metalloprotease inhibitors hydroxamate, methanethiolate, and methylphosphoramidate to a model coordination site occurring in several Zn2+ metalloproteases, including thermolysin. This was carried out using both the SIBFA (sum of interactions between fragments ab

initio-computed) molecular mechanics and the SCF/MP2 procedures for the purpose of evaluating SIBFA as a metalloenzyme modeling tool, The energy-minimized structures were closely similar to the **X-ray crystallographic** structures of related thermolysin-inhibitor complexes. We found that selectivity between alternative geometries and between inhibitors usually stemmed from multiple interaction components included in SIBFA. The binding strength sequence is hydroxamate > methanethiolate greater than or equal to methylphosphoramidate from multiple interaction components included in SIBFA. The trends in interaction energy components, rankings, and preferences for mono-or bidentate binding were consistent in both computational procedures, We also compared the Zn2+ vs. Mg2+ selectivities in several other polycoordinated sites having various "hard" and "soft" qualities, This included a hexahydrate, a model representing Mg2+/Ca2+ binding sites, a chlorophyll-like structure, and a zinc finger model, The latter three favor Zn2+ over Mg2+ by a greater degree than the hydrated state, but the selectivity varies widely according to the ligand "softness." SIBFA was able to match the ab initio binding energies by <2%, with the SIBFA terms representing dispersion and charge-transfer contributing the most to Zn2+/Mg2+ selectivity. These results showed this procedure to be a very capable modeling tool for metalloenzyme problems, in this case giving valuable information about details and limitations of "hard" and "soft" selectivity trends. (C) 1998 Wiley-Liss, Inc.

L44 ANSWER 28 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on
STN
ACCESSION NUMBER: 1997:562465 SCISEARCH Full-text
THE GENUINE ARTICLE: XM538
TITLE: gem-Dialkyl succinic acids: A novel class of inhibitors for carboxypeptidases
AUTHOR: AsanteAppiah E (Reprint); Seetharaman J; Sicheri F; Yang D
S C; Chan W W C
CORPORATE SOURCE: MCMASTER UNIV, DEPT BIOCHEM, HAMILTON, ON L8N 3Z5, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: BIOCHEMISTRY, (22 JUL 1997) Vol. 36, No. 29, pp. 8710-8715
ISSN: 0006-2960.
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 30
ENTRY DATE: Entered STN: 1997
Last Updated on STN: 1997
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB gem-Dimethylsuccinic add and its higher homolog, 2-methyl-2-ethylsuccinic acid (MESA) are highly potent inhibitors of both carboxypeptidase A (CPA) and B. The inhibition constant of MESA for CPA (0.11 mu M for the racemic mixture) is remarkable

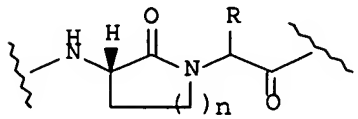
considering the relatively simple structure of the compound. The molecular feature which is crucial for high affinity binding to both carboxypeptidases appears to be the nonpolar gem-dialkyl locus. The structure of the complex between MESA and CPA has been determined by **X-ray crystallography** to 2.0 Angstrom resolution and shows the R enantiomer of the inhibitor to be bound in a generally substrate-like manner, The carboxymethyl group is coordinated to the Zn ion in the active site, and the gem-dialkyl locus corresponds in position to the alpha-carbon of the C-terminal amino acid in a peptide substrate, The methyl group of the inhibitor occupies a cavity in the enzyme which is apparently not filled upon substrate-binding, We postulate that this cavity (the alpha-methyl hole) is designed to allow the proximal Glu-270 residue to undergo a critical movement during catalysis, The hydrophobic nature of the above cavity may play a role in modulating the reactivity of this residue. These results suggest that similar cenophilic (empty-loving) inhibitors may be found for other enzymes.

L44 ANSWER 29 OF 76 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1998035576 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9369067
TITLE: A case of infiltration of scar of sarcoidosis after blepharoplasty.
AUTHOR: Takahashi J; Morishima T; Satoh Y; Hashimoto S
CORPORATE SOURCE: Department of Ophthalmology, Itabashi-ku Medical Association Hospital, Japan.
SOURCE: Nippon Ganka Gakkai zasshi, (1997 Oct) 101 (10) 832-6. Journal code: 7505716. ISSN: 0029-0203.
PUB. COUNTRY: Japan
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980130
Last Updated on STN: 19980130
Entered Medline: 19980121

AB A case of a 28-year-old woman with infiltration of sarcoidosis scar tissue after blepharoplasty is reported. Nodules developed two times in her right upper eyelid about 1 and 2 years after blepharoplasty of both eyes and they were resected each time, but eruption recurred. Ophthalmic examination revealed aqueous flare and cells, snowball vitreous opacities, and retinal periphlebitis. A chest **X-ray** disclosed bilateral hilar lymphadenopathy (BHL). Laboratory studies showed an elevation of the serum **angiotensin converting enzyme** (ACE). Light microscopy revealed epithelioid granuloma with no caseation necrosis in a biopsy specimen, Viewing through polarized light demonstrated **crystalline**-like foreign bodies with bi-refringence in the epithelioid granuloma. Electron microscopic **X-ray** microanalysis confirmed these foreign bodies to be composed of Si, Mg, and O. These findings indicate that this skin lesion was caused by an infiltration of sarcoidosis scar tissue.

L44 ANSWER 30 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 9

ACCESSION NUMBER: 1997:127102 CAPLUS Full-text
DOCUMENT NUMBER: 126:118181
TITLE: Stereoselective Synthesis of Freidinger Lactams Using
Oxaziridines Derived from Amino Acids
AUTHOR(S): Wolfe, Michael S.; Dutta, Dinah; Aube, Jeffrey
CORPORATE SOURCE: Department of Medicinal Chemistry, University of Kansas, Lawrence, KS, 66045-2506, USA
SOURCE: Journal of Organic Chemistry (1997), 62(3), 654-663
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:118181
GI



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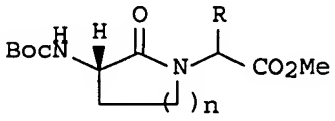
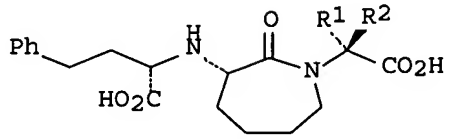


II



III

AB Conformationally restrained dipeptidyl lactams are building blocks for the synthesis of peptidomimetics, including Freidinger lactams I. Few synthetic methodologies toward such moieties allow for incorporation of a stereodefined substituent on the ring nitrogen (i.e., corresponding to an amino acid side chain). Enantiopure Freidinger lactams were obtained by (1) condensation of (S)-tert-butoxycarbonyl (Boc)-protected 2-aminocycloalkanones with com. available α-amino esters, (2) oxidation of the resulting imines with mCPBA to give spirocyclic oxaziridines, and (3) photorearrangement. Conformational analyses of seven- and eight-membered dipeptidyl lactams II (R = amino acid side chain, n = 3, 4) by NMR and by **x-ray crystallog.** are described. The utility of this chemical was illustrated by the synthesis of III (R1 = CH2Ph, CH2CHMe2, R2 = H; R1 = H, R2 = CH2Ph, CH2CHMe2) as potential **angiotensin converting enzyme** (ACE) inhibitors.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 31 OF 76 MEDLINE on STN
ACCESSION NUMBER: 97198287 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9046341
TITLE: Meta-substituted benzofused macrocyclic lactams as zinc metalloprotease inhibitors.

AUTHOR: Ksander G M; de Jesus R; Yuan A; Ghai R D; McMartin C; Bohacek R
CORPORATE SOURCE: Research Department, CIBA-GEIGY Corporation, Summit, New Jersey 07901, USA.
SOURCE: Journal of medicinal chemistry, (1997 Feb 14) 40 (4) 506-14.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970407
Last Updated on STN: 19970407
Entered Medline: 19970326

AB The design, synthesis, and biochemical profile of meta-substituted benzofused macrocyclic lactams are described. The meta-substituted benzofused macrocyclic lactams were designed to have a degree of flexibility allowing the amide bond to occupy two completely different conformations while maintaining sufficient rigidity to allow for strong interaction between enzyme and inhibitor. Using TFIT, a novel molecular superimposition program, it was shown that the meta analogs could be readily superimposed onto our ACE inhibitor template whereas no low-energy superimpositions of the ortho-substituted macrocycles could be found. The macrocycles were prepared by tethering aldehyde 1 derived from S-glutamic acid or S-aspartic acid to a meta-substituted phosphonium bromide 2. Homologation to a monocarboxylic acid methyl ester malonate followed by deprotection and cyclization gave the macrocyclic frame. Further manipulation gave the desired compounds. Unlike the ortho-substituted benzofused macrocyclic lactams described in the previous paper which are selective NEP inhibitors, the meta-substituted compounds are dual inhibitors of both NEP and ACE. The most potent member of this new series, compound 16a, inhibited both enzymes with an IC50 = 8 nM in NEP and 4 nM in ACE.

L44 ANSWER 32 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on
STN
ACCESSION NUMBER: 1997:702699 SCISEARCH Full-text
THE GENUINE ARTICLE: XX060
TITLE: QXP: Powerful, rapid computer algorithms for structure-based drug design
AUTHOR: McMartin C (Reprint); Bohacek R S
CORPORATE SOURCE: NOVARTIS PHARMACEUT CORP, RES DEPT, SUMMIT, NJ 07901 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF COMPUTER-AIDED MOLECULAR DESIGN, (JUL 1997) Vol. 11, No. 4, pp. 333-344.
ISSN: 0920-654X.
PUBLISHER: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA
DORDRECHT, NETHERLANDS.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 50
ENTRY DATE: Entered STN: 1997

Last Updated on STN: 1997
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB New methods for docking, template fitting and building pseudo-receptors are described. Full conformational searches are carried out for flexible cyclic and acyclic molecules. QXP (quick explore) search algorithms are derived from the method of Monte Carlo perturbation with energy minimization in Cartesian space. An additional fast search step is introduced between the initial perturbation and energy minimization. The fast search produces approximate low-energy structures, which are likely to minimize to a low energy. For template fitting, QXP uses a superposition force field which automatically assigns short-range attractive forces to similar atoms in different molecules. The docking algorithms were evaluated using **X-ray** data for 12 protein-ligand complexes. The ligands had up to 24 rotatable bonds and ranged from highly polar to mostly nonpolar. Docking searches of the randomly disordered ligands gave rms differences between the lowest energy docked structure and the energy-minimized **X-ray** structure, of less than 0.76 Angstrom for 10 of the ligands. For all the ligands, the rms difference between the energy-minimized **X- ray** structure and the closest docked structure was less than 0.4 Angstrom, when parts of one of the molecules which are in the solvent were excluded from the rms calculation. Template fitting was tested using four ACE inhibitors. Three ACE templates have been previously published. A single run using QXP generated a series of templates which contained examples of each of the three. A pseudo-receptor, complementary to an ACE template, was built out of small molecules, such as pyrrole, cyclo-pentanone and propane. When individually energy minimized in the pseudo-receptor, each of the four ACE inhibitors moved with an rms of less than 0.25 Angstrom. After random perturbation, the inhibitors were docked into the pseudo-receptor. Each lowest energy docked structure matched the energy-minimized geometry with an rms of less than 0.08 Angstrom. Thus, the pseudo-receptor shows steric and chemical complementarity to all four molecules. The QXP program is reliable, easy to use and sufficiently rapid for routine application in structure-based drug design.

L44 ANSWER 33 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1997:187777 SCISEARCH Full-text
THE GENUINE ARTICLE: WL042
TITLE: Aminophosphonic and aminoboronic acids as key elements of a transition state analogue inhibitor of enzymes
AUTHOR: Hiratake J (Reprint); Oda J
CORPORATE SOURCE: KYOTO UNIV, CHEM RES INST, UJI, KYOTO 611, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: BIOSCIENCE BIOTECHNOLOGY AND BIOCHEMISTRY, (FEB 1997) Vol. 61, No. 2, pp. 211-218.
ISSN: 0916-8451.
PUBLISHER: JAPAN SOC BIOSCI BIOTECHN AGROCHEM, JAPAN ACAD SOC CTR BLDG, 2-4-6 YAYOI BUNKYO-KU, TOKYO 113, JAPAN.
DOCUMENT TYPE: General Review; Journal

FILE SEGMENT: LIFE; AGRI
LANGUAGE: English
REFERENCE COUNT: 66
ENTRY DATE: Entered STN: 1997
Last Updated on STN: 1997
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Amino acid analogues are of considerable interest as inhibitors of enzymes involved in amino acid and peptide metabolism, In particular, alpha-aminoalkylphosphonic acids and alpha-aminoalkylboronic acids, in which the carboxyl group of amino acids is replaced by a phosphonic acid or boronic acid function, respectively, constitute a unique class of amino acid mimics from which a number of potent enzyme inhibitors have been prepared, The inhibitory activity mainly stems from the fact that the tetrahedral phosphonic moiety or the tetrahedral adduct of electrophilic boronic acid is a good mimic of the putative tetrahedral transition state or intermediate encountered in the enzymatic hydrolysis or formation of peptides, Since the peptide hydrolysis and formation invariably involves the tetrahedral high energy species in the course of the reaction, these amino acid mimics serve as a general key element for inhibitors of a broad spectrum of proteases and peptide ligases, The transition state analogy of aminophosphonic- and aminoboronic acid-derived inhibitors also gives a clue to the detailed reaction mechanisms of the enzymes by **X- ray crystallographic** and NMR analysis of the enzyme-inhibitor complex.

L44 ANSWER 34 OF 76 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 97290481 EMBASE Full-text
DOCUMENT NUMBER: 1997290481
TITLE: Chemistry of bifunctional photoprobes II. Chemical and photochemical modification of **angiotensin converting enzyme** inhibitors: Implications in the development of cardiac radionuclide imaging agents.
AUTHOR: Pandurangi R.S.; Lusiak P.; Kuntz R.R.; Sun Y.; Weber K.T.
CORPORATE SOURCE: R.S. Pandurangi, 123 Chemistry Building, Department of Chemistry, University of Missouri, Columbia, MO 65211, United States. spandura@mail.state.Mo.US.
SOURCE: Bioorganic Chemistry, (1997) Vol. 25, No. 2, pp. 77-87. .
Refs: 30
ISSN: 0045-2068 CODEN: BOCMBM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 023 Nuclear Medicine
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 971009
Last Updated on STN: 971009

AB The synthesis and biological activity of functionalized lisinopril, a potent **angiotensin converting enzyme** (ACE) inhibitor is described. Selective functionalization of lisinopril is achieved at the secondary

amino position by a photochemical method, whereas esterfication of the carboxylic groups and modification at the primary amino group is achieved by chemical methods. Autoradiographic investigations using competitive 125I radioactive binding assays with the modified lisinopril reveal that the terminal amino group modification enhanced the binding to ACE, whereas the secondary amino group functionalization did not differ significantly from the binding properties of native lisinopril. However, esterification of the carboxyl groups reduced the inhibitory potentency from nM to μM. These results suggest that lisinopril can be derivatized with preservation of inhibition potency toward ACE. These modifications may find utility in the development of photoaffinity labeling agents for ACE or to incorporate bifunctional chelating agents carrying diagnostic radiometals for the development of cardiac imaging agents.

L44 ANSWER 35 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1997:56121 SCISEARCH Full-text
THE GENUINE ARTICLE: WB915
TITLE: Stereochemistry in inactivation of carboxypeptidase A. Structural analysis of the inactivated carboxypeptidase A by an enantiomeric pair of 2-benzyl-3,4-epoxybutanoic acids
AUTHOR: Ryu S E (Reprint); Choi H J; Kim D H
CORPORATE SOURCE: KOREA RES INST BIOSCI & BIOTECHNOL, PROT ENGN RES DIV, POB 115, TAEJON 305600, SOUTH KOREA (Reprint); POHANG UNIV SCI & TECHNOL, CTR BIOFUNCT MOL, POHANG 790784, SOUTH KOREA; POHANG UNIV SCI & TECHNOL, DEPT CHEM, POHANG 790784, SOUTH KOREA
COUNTRY OF AUTHOR: SOUTH KOREA
SOURCE: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, (8 JAN 1997) Vol. 119, No. 1, pp. 38-41.
ISSN: 0002-7863.
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: PHYS; LIFE
LANGUAGE: English
REFERENCE COUNT: 41
ENTRY DATE: Entered STN: 1997
Last Updated on STN: 1997

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The **X-ray crystal** structure of inactivated carboxypeptidase A by (2R,3S)-2-benzyl-3,4-epoxybutanoic acid, a pseudomechanism-based inactivator, was determined to show that the carboxylate of Glu-270 at the active site of the enzyme is covalently modified: the inhibitor is tethered to the carboxylate forming an ester linkage which is brought about by the attack of the carboxylate on the oxirane ring of the inhibitor. Examination of the **crystal** structure in comparison with that inactivated by its enantiomer, (2S,3R)-2-benzyl-3,4-epoxybutanoic acid, shows that the two

inhibitors are bound covalently to the enzyme in a symmetrical fashion. An explanation for the lack of inactivating activity found previously with(2R,3R)- as well as (2S,3S)-2-benzyl-3,4-epoxybutanoic acids was offered.

L44 ANSWER 36 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 1996:494199 CAPLUS Full-text
DOCUMENT NUMBER: 125:184878
TITLE: Three-Dimensional Models of ACE and NEP Inhibitors and
Their Use in the Design of Potent Dual ACE/NEP Inhibitors
AUTHOR(S): Bohacek, Regine; De Lombaert, Stephane; McMartin, Colin; Priestle, John; Gruetter, Markus
CORPORATE SOURCE: Pharmaceuticals Division, Ciba-Geigy Corporation, Summit, NJ, 07901, USA
SOURCE: Journal of the American Chemical Society (1996), 118(35), 8231-8249
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A composite template for **angiotensin converting enzyme** (ACE, EC 2.4.15.1) inhibitors and a hypothetical model of the active site of neutral endopeptidase (NEP, EC 3.4.24.11) have been constructed and used to guide the design of dual ACE/NEP inhibitors. For the ACE template, a new computer program was used to flexibly superimpose potent, conformationally restricted ACE inhibitors. This program, which only considers the structures of the ligands, generated three possible templates. It was possible to evaluate the plausibility of these templates because new **x-ray** data is extending the authors knowledge of the binding of ligands to zinc metalloproteases. The authors have found that the available **x-ray** structures of inhibitors complexed to different zinc metalloproteases share certain conformational features. In each complex, the regions between the catalytic zinc and the P1' side chain were found to have almost the same geometry. This geometry appears to be dictated by the mechanism of catalysis. Only one of the templates displays this geometry and is, therefore, proposed as a pharmacophore for ACE. To simulate NEP, the authors used the **crystal** structure of the active site of thermolysin (EC 3.4.24.4). These models of ACE and NEP predict that the conformation an inhibitor must adopt to bind to ACE differs from that required for binding to NEP. The authors have designed inhibitors in which conformationally restricted sections are linked by a flexible hinge, allowing the mols. to adapt to the conformation required by each enzyme. One of these inhibitors, a tricyclic α-thiol, CGS 28106 (I), was found to inhibit both ACE and NEP with an IC50 of 40 and 48 nM, resp. The models predict that I binds to the S1', S2', and S3' subsites of NEP and thermolysin and to the S1, S1', and S2' subsites of ACE. The predicted mode of binding of I to thermolysin was exptl. verified by the determination of the **x-ray crystal** structure of the thermolysin/I complex. This is the first reported three-dimensional structure of an α-thiol bound to a zinc metalloprotease. Except for a single NEP inhibitor, the models the authors propose for ACE and NEP are able to differentiate between active

and inactive compds. reported in the present as well as other studies of dual ACE/NEP inhibition.

L44 ANSWER 37 OF 76 MEDLINE on STN
ACCESSION NUMBER: 96242782 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8652101
TITLE: Hippuryl-L-histidyl-L-leucine, a substrate for **angiotensin converting enzyme.**
AUTHOR: Vrielink A; Obel-Jorgensen A; Codding P W
CORPORATE SOURCE: Department of Biochemistry, McGill University, Montreal, Quebec, Canada.
SOURCE: Acta crystallographica. Section C, Crystal structure communications, (1996 May 15) 52 (Pt 5) 1300-2.
Journal code: 8305826. ISSN: 0108-2701.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960808
Last Updated on STN: 19960808
Entered Medline: 19960726

AB The tripeptide **crystallizes** as a zwitterion with a protonated histidyl ring and the C-terminus ionized and with five water molecules of hydration (C21H27N5O5(.5)H2O). The tripeptide adopts an all trans extended conformation with the histidine and phenyl rings parallel to one another. The C-terminus coils into a helical conformation. An intramolecular hydrogen bond between the C-terminus and the N delta atom of the histidine ring stabilizes the helical conformation. The principal torsion angles are phi 1 = -67.7 (8), psi 1 = 140.8 (5), omega 1 = 171.0 (6), phi 2 = -156.5 (5), psi 2 = 162.7 (5), omega 2 = 175.0 (5), phi 3 = -96.4 (6), psi T1 = 14.5 (8) and psi T2 = -164.6 (6) degrees [IUPAC-IUB Commission on Biochemical Nomenclature (1970). J. Mol. Biol. 52, 1-17]. The tripeptides are linked in infinite chains through a short intermolecular hydrogen bond between the C-terminal carboxylate group and the protonated histidyl N epsilone atom.

L44 ANSWER 38 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on
STN
ACCESSION NUMBER: 1996:548919 SCISEARCH Full-text
THE GENUINE ARTICLE: UY418
TITLE: Structural versatility of peptides from C-alpha,C-alpha-disubstituted glycines: **Crystal** -state conformational analysis of peptides from C-alpha-methylhomophenylalanine, (alpha Me)Hph
AUTHOR: Doi M (Reprint); Ishida T; Polese A; Formaggio F; Crisma M; Toniolo C; Broxterman Q B; Kamphuis J
CORPORATE SOURCE: UNIV PADUA, DEPT ORGAN CHEM, CNR, BIOPOLYMER RES CTR, I-35131 PADUA, ITALY; OSAKA UNIV PHARMACEUT SCI, OSAKA 580, JAPAN; DSM RES BV, BIOORGAN CHEM SECT, NL-6160 MD GELEEN, NETHERLANDS
COUNTRY OF AUTHOR: ITALY; JAPAN; NETHERLANDS
SOURCE: INTERNATIONAL JOURNAL OF PEPTIDE AND PROTEIN RESEARCH, (JUN 1996) Vol. 47, No. 6, pp. 491-497.

ISSN: 0367-8377.
PUBLISHER: MUNKSGAARD INT PUBL LTD, 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 68
ENTRY DATE: Entered STN: 1996
Last Updated on STN: 1996
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The molecular and **crystal** structures of the C-alpha-tetrasubstituted, delta-branched alpha-amino acid C-alpha-methylhomophenylalanine, H-D-(alpha Me)Hph-OH, and three peptides (to the pentamer level), including the homotripeptide, have been determined by **X-ray** diffraction. The peptides are Z-L-(alpha Me)Hph-(L-Ala)(2)-OMe, pBrBz-[D-(alpha Me)Hph](3)-OtBu and Ac-(Aib)(2)-L-(alpha Me)Hph-(Aib)(2)-OtBu. All the (alpha Me)Hph residues prefer phi,psi torsion angles in the helical region of the conformational map. The two terminally blocked tripeptides adopt a beta-bend conformation stabilized by a 1<--4 C=O ... H-N intramolecular H-bond. The terminally blocked pentapeptide is folded in a regular 3(10)-helix. In general, the relationship between (alpha Me)Hph alpha-carbon chirality and helix handedness is the same as that exhibited by protein amino acids. A comparison is also made with the conclusions extracted from published work on peptides from other types of C-alpha-alkylated aromatic alpha-amino acids. (C) Munksgaard 1996.

L44 ANSWER 39 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:49736 CAPLUS Full-text
DOCUMENT NUMBER: 126:114851
TITLE: Neutral endopeptidase-24.11: structure, and design and clinical use of inhibitors
AUTHOR(S): Beaumont, Ann; Fournie-Zaluski, Marie-Claude; Roques, Bernard P.
CORPORATE SOURCE: Faculte de Pharmacie, Univ. Rene Descartes, Paris, 75270, Fr.
SOURCE: Zinc Metalloproteases in Health and Disease (1996), 105-129. Editor(s): Hooper, Nigel M. Taylor & Francis: London, UK.
CODEN: 63WOAB
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review with .apprx.100 refs. Neutral endopeptidase-24.11 (NEP, neprilysin, EC 3.4.24.11) is a zinc metallopeptidase with a thermolysin-like specificity for cleaving peptides on the N-terminal side of hydrophobic residues. The cloning of this ectoenzyme and subsequent site-directed mutagenesis expts. have shown that, as well as having a similar specificity to thermolysin, it also has a similar active site organization, and **x-ray crystallog.** data for the bacterial enzyme has been invaluable for designing NEP inhibitors. The clin. interest in these inhibitors derives from the actions of NEP, in conjunction with aminopeptidase N (APN), in degrading the enkephalins and also its role in degrading atrial natriuretic peptide. Dual NEP/APN inhibitors

completely block enkephalin metabolism and have strong antinociceptive properties. Similarly, dual inhibitors of NEP and **angiotensin converting enzyme** (ACE) are potent antihypertensives, resulting from simultaneously increasing the circulating levels of atrial natriuretic peptide, due to NEP inhibition, and decreasing the circulating levels of angiotensin II, due to ACE inhibition. The design of these dual inhibitors and their potential advantages over currently available analgesics and antihypertensives is discussed.

L44 ANSWER 40 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1995:194041 SCISEARCH Full-text
THE GENUINE ARTICLE: QL870
TITLE: STRUCTURE AND CONFORMATION OF (1S,2R)-CIS-2-[HYDROXYAMINOCARHONYLMETHYL(N-METHYL)AMINOCARBONYL]CYCLOHEXANECARBOXYLIC ACID - **X-RAY**, NMR AND MOLECULAR MECHANICS STUDIES
AUTHOR: DIBUGNO C (Reprint); COLOMBANI S M; DAPPORTO P; GIORGI R; PAOLI P
CORPORATE SOURCE: LAG BUIDOTT SPA, VIA LIVORNESE 402, I-56122 PISA, ITALY (Reprint); UNIV FLORENCE, DIPARTIMENTO ENERGET, I-50139 FLORENCE, ITALY
COUNTRY OF AUTHOR: ITALY
SOURCE: JOURNAL OF THE CHEMICAL SOCIETY-PERKIN TRANSACTIONS 2, (MAR 1995) No. 3, pp. 609-613.
ISSN: 0300-9580.
PUBLISHER: ROYAL SOC CHEMISTRY, THOMAS GRAHAM HOUSE SCIENCE PARK MILTON ROAD, CAMBRIDGE, CAMBS, ENGLAND CB4 4WF.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: PHYS; LIFE
LANGUAGE: English
REFERENCE COUNT: 19
ENTRY DATE: Entered STN: 1995
Last Updated on STN: 1995

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The structural characterization of idrapril, (1S,2R)-cis-2-[hydroxyaminocarbonylmethyl(N-methyl)-aminocarbonyl] cyclohexanecarboxylic acid (4), a novel ACE-inhibitor and its related benzyloxy derivative (3) has been carried out by NMR studies. The **crystal** structure of 3 has been determined by **X-ray** diffraction. The NMR spectra indicate the presence of two cis and trans isomers with respect to the amide bond at room temperature, with rotational barriers of 70 kJ mol(-1). The preferred conformation of these compounds is the trans rotamer with the carboxylic moiety in the equatorial orientation. Conformational studies in aqueous solution have been reported for idrapril as a function of pH and the equilibrium constant has been determined. The results suggest the presence of intramolecular hydrogen bonds, as is confirmed by molecular mechanics calculations.

L44 ANSWER 41 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on

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ACCESSION NUMBER: 1995:549641 SCISEARCH Full-text
THE GENUINE ARTICLE: RP971
TITLE: ZINC-DIRECTED INHIBITORS FOR ZINC PROTEINASES
AUTHOR: FEINBERG H (Reprint); GREENBLATT H M; BEHAR V; GILON C; COHEN S; BINO A; SHOHAM G
CORPORATE SOURCE: HEBREW UNIV JERUSALEM, INST CHEM, IL-91904 JERUSALEM, ISRAEL; HEBREW UNIV JERUSALEM, STRUCT CHEM & BIOL LAB, IL-91904 JERUSALEM, ISRAEL
COUNTRY OF AUTHOR: ISRAEL
SOURCE: ACTA CRYSTALLOGRAPHICA SECTION D-BIOLOGICAL CRYSTALLOGRAPHY, (1 JUL 1995) Vol. 51, Part 4, pp. 428-449

ISSN: 0907-4449.
PUBLISHER: MUNKSGAARD INT PUBL LTD, 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: PHYS; LIFE
LANGUAGE: English
REFERENCE COUNT: 105
ENTRY DATE: Entered STN: 1995
Last Updated on STN: 1995

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Zinc proteinases have been recognized as a distinct class of proteolytic enzymes in which at least one ion of zinc is involved directly in catalysis. This family includes a growing number of biologically important enzymes which are attractive targets for rational drug design. In this paper we examine the special features of the zinc binding environment of these enzymes in order to gain information which could be useful in the preparation of 'zinc-directed' selective inhibitors. Carboxypeptidase A (CPA) is presented as a model for one class of zinc proteinases, and the active-site zinc and its interactions are examined with the primary focus on geometrical considerations. The three-dimensional structure of the native and apoenzyme are discussed, together with the high-resolution structure of several enzyme-inhibitor complexes. This paper will first present a structural analysis of CPA derivatives and then discuss a series of zinc model compounds which have been prepared and characterized in order to examine the ligand and geometrical preferences of the zinc in an unstrained system. **X- ray crystallography** (macromolecular and small molecule) is the main experimental method used for the structural analyses, while complementary computational methods have been used for the examination of electrostatic potentials. The results from the various experimental efforts are assembled in order to draw general conclusions on the potential use of the zinc ion as the primary target for inhibitor binding. The results of these studies suggest that the zinc ion is important for both the binding and the catalytic activation of the substrate as well as for stabilization of the tetrahedral reaction intermediate.

L44 ANSWER 42 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 11
ACCESSION NUMBER: 1995:1006006 CAPLUS Full-text
DOCUMENT NUMBER: 124:55023

TITLE: Automated chemical hypothesis generation and database searching with Catalyst
AUTHOR(S): Sprague, Peter W.
CORPORATE SOURCE: Mol. Simulations Inc., Pennington, NJ, 08534, USA
SOURCE: Perspectives in Drug Discovery and Design (1995), 3(De Novo Design), 1-20
CODEN: PDDDEC; ISSN: 0928-2866
PUBLISHER: ESCOM
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Catalyst program represents a new approach that focuses on modeling the drug-receptor interaction from the point of view of the receptor, using information derived only from the drug. Mols. are described as collections of chemical functions arranged in three-dimensional space. Conformational flexibility is modeled by creating multiple conformers, judiciously prepared to emphasize representative coverage over a specified energy range. A training set, consisting of approx. 20 mols. ranging in activity over four orders of magnitude, becomes the information set used to derive a hypothesis, a minimal collection of chemical features common across the set that explains the observed activity. A hypothesis can serve as an electronic query for searching 3D databases of structures for compds. that, fitting its constraints, are potential leads for further development. The method was applied in different ways to four problems in medicinal chemical, i.e., **angiotensin converting enzyme** (ACE), protein farnesyl transferase (PFT), human immunodeficiency virus (HIV) protease (PHIV), and HIV reverse transcriptase (RTHIV) inhibition. From a training set of 20 small peptides with ACE inhibitory activity, a five-featured hypothesis was found that is predictive for inhibitors outside of the set. From a training set of 20 CaaX box tetrapeptides, a hypothesis for PFT inhibition was computed that explains the activities of non-peptide inhibitors reasonably well. Representative compds. from three structurally different classes of RTHIV inhibitors were used to generate a simple four-featured hypothesis that suggests how all three classes could bind to the same receptor. Finally, an enzyme-bound conformation of SB-203386, an inhibitor of PHIV, determined by **X-ray crystallog** . was used to manually construct a hypothesis. This was then used to search 3D databases for structures of interest as inhibitors of the enzyme.

L44 ANSWER 43 OF 76 MEDLINE on STN
ACCESSION NUMBER: 94355548 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8075303
TITLE: Design, synthesis and enzyme inhibitory activities of new trifluoromethyl-containing inhibitors for **angiotensin converting enzyme.**
AUTHOR: Ojima I; Jameison F A; Pete B; Radunz H; Schittenhelm C; Lindner H J; Emith A E
CORPORATE SOURCE: Department of Chemistry, State University of New York at Stony Brook 11794-3400.
SOURCE: Drug design and discovery, (1994 Feb) 11 (2) 91-113. Journal code: 9200627. ISSN: 1055-9612.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 19941013
Last Updated on STN: 19941013
Entered Medline: 19941006

AB A series of trifluoromethyl-containing analogs of captopril as well as analogs and homologs of enalaprilat were synthesized and evaluated for inhibition of **angiotensin converting enzyme** (ACE). It was found that direct substitution of trifluoromethyl for methyl produced a very potent captopril analog with an IC50 of 3 x 10(-10) M in vitro. Hydrophobicity and conformational effects of trifluoromethyl group are among the reasons accounting for this activity. Structure-activity relationship is studied based on molecular mechanics calculations using a II-SCF-molecular mechanics program (PIMM) as well as SYBYL molecular mechanics program. It was found that simultaneous incorporation of trifluoromethyl and an indoline residue unexpectedly yielded a less potent captopril analog (IC50 = 8 x 10(-8) M). Enalaprilat analogs derived from replacement of the alanine residue with trifluoronorvaline and trifluoronorleucine residues gave moderately potent compounds (IC50 = 2-6 x 10(-8) M). The structure-activity relationship for these fluoroenalaprilat analogs is discussed in comparison with known analogs.

L44 ANSWER 44 OF 76 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 94114513 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8286362
TITLE: Inhibition of thermolysin and neutral endopeptidase 24.11 by a novel glutaramide derivative: **X-ray** structure determination of the thermolysin-inhibitor complex.
AUTHOR: Holland D R; Barclay P L; Danilewicz J C; Matthews B W; James K
CORPORATE SOURCE: Howard Hughes Medical Institute, University of Oregon, Eugene 97403.
CONTRACT NUMBER: GM20066 (NIGMS)
SOURCE: Biochemistry, (1994 Jan 11) 33 (1) 51-6.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199402
ENTRY DATE: Entered STN: 19940312
Last Updated on STN: 20000303
Entered Medline: 19940224

AB Determination of the **X-ray** structure of thermolysin-inhibitor complexes has proven useful in aiding our understanding of the mode of binding of inhibitors of related, physiologically important, mammalian zinc peptidases including neutral endopeptidase EC 3.4.24.11 and **angiotensin-converting enzyme**. Here we describe the mode of binding to **crystalline** thermolysin of N-[1-(2(R,S)-carboxy-4-phenylbutyl)-cyclopentylcarbonyl]-(S) -tryptophan (CCT). CCT is an analogue of both candoxatrilat, a potent inhibitor of neutral endopeptidase 24.11, and of the 5-indanyl ester prodrug candoxatril, which is under clinical evaluation as a potential therapy for congestive heart failure. CCT differs from the previously studied N-carboxyalkyl dipeptide CLT [N-(S)-(1-carboxy-3-phenylpropyl)-(S)-leucyl-(S)-tryptophan] in several

important respects. It has a highly constrained gem-cyclopentyl P1' substituent and lacks the characteristic imino nitrogen substituent of CLT. The structure determination shows that, notwithstanding the conformational influence of the gem-cyclopentyl substituent, CCT binds within the active site of thermolysin in a similar manner to CLT. Although the characteristic hydrogen bond between the imino nitrogen of CLT and thermolysin is absent in CCT, the affinities of the two inhibitors for the enzyme are virtually identical. These results illustrate the importance of considering not only those hydrogen bonds that are formed in an enzyme-ligand complex but also the other hydrogen bonds that may be lost due to desolvation of the enzyme and ligand on formation of the complex. In addition, the overall conformational demands placed upon a ligand in order to achieve receptor interaction may be critically important.

L44 ANSWER 45 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on
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ACCESSION NUMBER: 1993:517858 SCISEARCH Full-text
THE GENUINE ARTICLE: LT674
TITLE: MECHANISTIC AND STEREOCHEMICAL STUDY OF PHENYLPYRUVATE TAUTOMERASE
AUTHOR: PIRRUNG M C (Reprint); CHEN J L; ROWLEY E G; MCPHAIL A T
CORPORATE SOURCE: DUKE UNIV, PM GROSS CHEM LAB, DEPT CHEM, DURHAM, NC 27708
(Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, (11 AUG 1993) Vol. 115, No. 16, pp. 7103-7110.
ISSN: 0002-7863.
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: PHYS; LIFE
LANGUAGE: English
REFERENCE COUNT: 56
ENTRY DATE: Entered STN: 1994
Last Updated on STN: 1994
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A variety of substrates and potential enol/enolate mimics for the product/transition state of the enzyme phenylpyruvate tautomerase (E.C. 5.3.2.1) have been prepared and studied. Their stereostructures have been secured by a combination of NMR spectroscopy based on vicinal H-F and H-C coupling constants and **X-ray crystallography** . On the basis of the inhibition by stereoisomeric substituted cinnamates, it has been concluded that the enzyme produces the thermodynamically less stable (E) enol via a syn tautomerization transition state. Free energy profiles for the reaction suggest that vinyl fluorides act as product analogues. Because amide and dicarboxylate enolate mimics are relatively poor inhibitors of the enzyme, it is believed that an enolate is not involved in the tautomerization process.

L44 ANSWER 46 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on

STN
ACCESSION NUMBER: 1994:485573 SCISEARCH Full-text
THE GENUINE ARTICLE: BZ58Z
TITLE: DETECTING METAL-METAL INTERACTIONS AND MEASURING DISTANCES
BETWEEN METAL CENTERS IN METALLOPROTEINS
AUTHOR: MARET W (Reprint)
CORPORATE SOURCE: HARVARD UNIV, SCH MED, CTR BIOCHEM & BIOPHYS SCI & MED, BOSTON, MA 02115 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: METALLOBIOCHEMISTRY, PART C, (1993) Vol. 226, Part C, pp.
594-618.
ISSN: 0076-6879.
PUBLISHER: ACADEMIC PRESS INC, 525 B STREET, SUITE 1900, SAN DIEGO, CA 92101-4495.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 118
ENTRY DATE: Entered STN: 1994
Last Updated on STN: 1994

L44 ANSWER 47 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on
STN
ACCESSION NUMBER: 1993:352098 SCISEARCH Full-text
THE GENUINE ARTICLE: LE407
TITLE: STRUCTURAL STUDIES OF THE ROLE OF THE ACTIVE-SITE METAL IN
METALLOENZYMES
AUTHOR: FEINBERG H (Reprint); GREENBLATT H M; SHOHAM G
CORPORATE SOURCE: HEBREW UNIV JERUSALEM, DEPT INORGAN CHEM, IL-91904 JERUSALEM, ISRAEL; HEBREW UNIV JERUSALEM, STRUCT CHEM & BIOL LAB, IL-91904 JERUSALEM, ISRAEL
COUNTRY OF AUTHOR: ISRAEL
SOURCE: JOURNAL OF CHEMICAL INFORMATION AND COMPUTER SCIENCES, (MAY-JUN 1993) Vol. 33, No. 3, pp. 501-516.
ISSN: 0095-2338.
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: PHYS
LANGUAGE: English
REFERENCE COUNT: 85
ENTRY DATE: Entered STN: 1994
Last Updated on STN: 1994
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB This paper describes several experimental and computational methods which are currently used in the structural analysis of metal-containing macromolecules. A specific family of proteolytic enzymes which contain a zinc cation in the active site was selected to demonstrate these methods. A range of studies using one example from this family of enzymes is described which serves to clarify the role of the metal in the overall protein structure and in the local conformation of the active site in the native enzyme, the metal-deficient enzyme, and the metal-substituted

enzyme and in complexes of the enzyme with various chemical analogues. The main experimental method described is **X-ray crystallography**, while computational methods for the examination of surface interactions and electrostatic potential effects are described briefly to complement the structural conclusions. The various experimental and computational results are, then assembled in order to draw general conclusions on the structure-function relationships of metalloproteins and in particular the role of the metal in metal-containing proteolytic enzymes. The results of these studies implicate the zinc ion in the binding and catalytic activation of the substrate and stabilization of the tetrahedral reaction intermediate. It appears that in this family of enzymes a divalent metal cation is important for the required catalytic arrangement of functional groups in the active site, especially the metal ligands. However, once an appropriate metal ion is coordinated, there is practically no effect of the particular metal ion bound on either the overall three dimensional structure of the enzyme or the local detailed structure of its active site.

L44 ANSWER 48 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on
STN
ACCESSION NUMBER: 1993:42059 SCISEARCH Full-text
THE GENUINE ARTICLE: KG629
TITLE: EXPLORATION OF NEUTRAL ENDOPEPTIDASE ACTIVE-SITE BY A SERIES OF NEW THIOL-CONTAINING INHIBITORS
AUTHOR: GOMEZMONTERREY I (Reprint); TURCAUD S; LUCAS E; BRUETSCHY L; ROQUES B P; FOURNIEZALUSKI M C
CORPORATE SOURCE: UNIV PARIS 05, UFR SCI PHARMACEUT & BIOL, CNRS, URA D 1500, INSERM, U266, F-75270 PARIS 06, FRANCE
COUNTRY OF AUTHOR: FRANCE
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (8 JAN 1993) Vol. 36, No. 1, pp. 87-94.
ISSN: 0022-2623.
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 44
ENTRY DATE: Entered STN: 1994
Last Updated on STN: 1994
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB With the aim of characterizing the active site of the neutral endopeptidase [EC 3.4.24.11 (NEP)] and especially its putative S1 subsite, two series of new thiol inhibitors designed to interact with the S1, S'1, and S'2 subsites of the enzyme have been synthesized. These molecules correspond to the general formula HSCH(R1)CH(R2)CONHCH(R3)COOH (series I) and HSCH(R1)CH(R2)-CONHCH(R3)CONHCH(R4)COOH(series II). Due to the synthetic pathway used, these inhibitors were obtained as mixtures of four stereoisomers. HPLC separation of the stereoisomers of 17 HSCH[CH2CH(CH3)2]CH(CH2Ph)CONHCH(CH3)COOH allowed the stereochemical dependence of the inhibitory potency to be

determined. The most active isomer 17b (IC50 = 3.6 nM) is assumed to have the S,S,S stereochemistry as deduced from both NMR and HPLC data. Although none of the inhibitors obtained were significantly more active than thiorphan, HSCH2CH(CH2Ph)-CONHCH2COOH (IC50 = 4 nM), which interacts only with the S'1 and S'2 subsites of NEP, their enhanced hydrophobicity is expected to improve their pharmacokinetic properties. An these compounds displayed low affinities for ACE (IC50s > 1 muM). The determination of the IC50s of two inhibitors of series II for NEP and for a mutated enzyme in which Arg102 was replaced by Glu102 allowed their mode of binding to the active site of NEP to be characterized. The R2 and R3 chains fit the S'1-S'2 subsites, while the R4 group is probably located outside the active site. Taken together these results indicate that the R1 chain of these inhibitors creates no additional stabilizing interactions with the active site of NEP. Two hypotheses may account for this: there is no hydrophobic S1 subsite in NEP or the inhibitors have structures which are too constrained for optimized interactions with the active site.

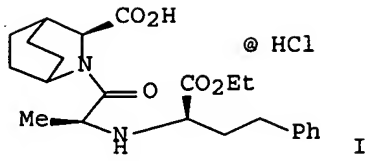
L44 ANSWER 49 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:573436 CAPLUS Full-text
DOCUMENT NUMBER: 119:173436
TITLE: Drug design based on the three-dimensional structure
AUTHOR(S): Hata, Tadashi
CORPORATE SOURCE: Anal. Metab. Res. Lab., Sankyo Co., Ltd., Tokyo, 140,
Japan
SOURCE: Nippon Kessho Gakkaishi (1993), 35(1), 7-13
CODEN: NKEGAF; ISSN: 0369-4585
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review, with 9 refs., on the 3-dimensional (D) arrangement of the topog. pharmacophoric pattern reflecting the 2-D matrix comprised of the interat. distances of the pattern, the geometrical matching system utilizing the 2-D matrix, application of the system to the study of **angiotensin -converting enzyme** inhibitors and anti-inflammatory drugs in Cambridge **crystal** data, and pharmacol. screening by **x-ray** structure anal.

L44 ANSWER 50 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on
STN
ACCESSION NUMBER: 1992:567212 SCISEARCH Full-text
THE GENUINE ARTICLE: JP593
TITLE: STRUCTURAL COMPARISON OF SULFODIIMINE AND SULFONAMIDE INHIBITORS IN THEIR COMPLEXES WITH ZINC ENZYMES
AUTHOR: CAPPALONGA A M (Reprint); ALEXANDER R S; CHRISTIANSON D W
CORPORATE SOURCE: UNIV PENN, DEPT CHEM, PHILADELPHIA, PA 19104 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (25 SEP 1992) Vol. 267, No. 27, pp. 19192-19197.
ISSN: 0021-9258.
PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650

ROCKVILLE PIKE, BETHESDA, MD 20814.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 48
ENTRY DATE: Entered STN: 1994
Last Updated on STN: 1994
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The three-dimensional structure of (L(-)-2-carboxy-3-phenylpropyl) methylsulfodiimine in its complex with the zinc metalloenzyme carboxypeptidase A has been determined at 2.25-angstrom resolution by **x-ray crystallographic** methods. This is the first example of a sulfodiimine-containing inhibitor binding to a zinc enzyme, and the structure of the enzyme-inhibitor complex reveals that the tetrahedral sulfodiimine group coordinates to the active site zinc ion in unidentate fashion. The zinc-coordinated nitrogen atom of the sulfodiimine group is also within hydrogen bonding distance to active site base Glu-270; presumably, the sulfodiimine is ionized and accepts a hydrogen bond from protonated Glu-270. The other sulfodiimine nitrogen accepts a hydrogen bond from Arg-127, and the inhibitor binds as a possible analogue of the tetrahedral transition state (or intermediate) in a promoted water pathway for peptide hydrolysis. The unidentate sulfodiimine-zinc binding mode observed in this enzyme-inhibitor complex is reminiscent of that observed in sulfonamide complexes with the zinc metalloenzyme carbonic anhydrase II, and the structural features of sulfodiimine- and sulfonamide-zinc interactions exhibit important similarities among recently determined structures of enzyme-inhibitor complexes: ionized nitrogens bind to zinc in each structure, and these nitrogens are engaged in hydrogen bond interactions with neighboring enzyme residues.

L44 ANSWER 51 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:124977 CAPLUS Full-text
DOCUMENT NUMBER: 118:124977
TITLE: Synthesis and conformational studies of Zabicipril (S 9650-3), a potent inhibitor of **angiotensin converting enzyme**
AUTHOR(S): Vincent, Michel; Pascard, Claudine; Cesario, Michele; Remond, Georges; Bouchet, Jean Paul; Charton, Yves; Laubie, Michel
CORPORATE SOURCE: Inst. Rech. Sevier, Suresnes, 92150, Fr.
SOURCE: Tetrahedron Letters (1992), 33(48), 7369-72
CODEN: TELEAY; ISSN: 0040-4039
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 118:124977
GI



I

AB The synthesis of the title compound I is described. The inhibitor of **Angiotensin Converting Enzyme** (ACE) contains 2-azabicyclo[2.2.2]octanecarboxylic acid, a bulky cyclic amino acid replacing the proline moiety present in most ACE inhibitors described in the literature. Structural anal. of I supports the hypothesis of preferred conformations for this type of pseudo peptidic mol., in solution (1H, 13C NMR) and in the solid state (**x-ray**).

L44 ANSWER 52 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1992:183013 SCISEARCH Full-text
THE GENUINE ARTICLE: HJ253
TITLE: **X-RAY CRYSTALLOGRAPHIC** STUDY OF COVALENTLY MODIFIED CARBOXYPEPTIDASE-A BY 2-BENZYL-3,4-EPOXYBUTANOIC ACID, A PSEUDOMECHANISM-BASED INACTIVATOR
AUTHOR: YUN M Y (Reprint); PARK C Y; KIM S S; NAM D Y; KIM S C; KIM D H
CORPORATE SOURCE: LUCKY LTD, CTR RES & DEV, POB 10 DAE DEOG DANJI, TAEJON 305343, SOUTH KOREA; POHANG INST SCI & TECHNOL, DEPT CHEM, POHANG 790600, SOUTH KOREA; POHANG INST SCI & TECHNOL, CTR BIOFUNCT MOLECULES, POHANG 790600, SOUTH KOREA
COUNTRY OF AUTHOR: SOUTH KOREA
SOURCE: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, (11 MAR 1992) Vol. 114, No. 6, pp. 2281-2282. ISSN: 0002-7863.
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036.
DOCUMENT TYPE: Note; Journal
FILE SEGMENT: PHYS; LIFE
LANGUAGE: English
REFERENCE COUNT: 27
ENTRY DATE: Entered STN: 1994
Last Updated on STN: 1994

L44 ANSWER 53 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1992:408467 CAPLUS Full-text
DOCUMENT NUMBER: 117:8467
TITLE: ACE-inhibitors [ACE = **angiotensin converting enzyme**] through the reaction of 4-hydroxy-2-butynoates with (S)-amino-acid

esters: a structural study on N-[3-(4'-dimethylaminophenyl)-1-(S)-ethoxycarbonyl-3-oxoprop-1-yl]-(S)-alanine benzyl ester

AUTHOR(S): Arcadi, Antonio; Cacchi, Sandro; Marinelli, Fabio; Adovasio, Victor; Nardelli, Mario

CORPORATE SOURCE: Dip. Chim., Ing. Chim. Mater., Univ. Aquila, L'Aquila, I-67100, Italy

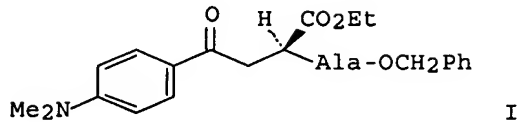
SOURCE: Gazzetta Chimica Italiana (1992), 122(3), 127-32
CODEN: GCITA9; ISSN: 0016-5603

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 117:8467

GI



I

AB The **crystal** and mol. structure of the title compound (I) has been determined by single **crystal x-ray** diffraction data collected using both Mo-Kα and Cu-Kα radiations. The results of the two analyses are in good agreement and confirm the NMR-based regiochem. of the conjugate addition step. The mol. has an extended conformation and the two asym. centers have the same S,S chirality. The conformation is discussed on the basis of the van der Waals-interactions.

L44 ANSWER 54 OF 76 MEDLINE on STN

ACCESSION NUMBER: 93125330 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 1480010

TITLE: Structural basis for the action of thermolysin.

AUTHOR: Tronrud D E; Roderick S L; Matthews B W

CORPORATE SOURCE: Institute of Molecular Biology, Howard Hughes Medical Institute, University of Oregon, Eugene 97403.

SOURCE: Matrix (Stuttgart, Germany). Supplement, (1992) 1 107-11.
Journal code: 9312140. ISSN: 0940-1199.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199302

ENTRY DATE: Entered STN: 19930226
Last Updated on STN: 20000303
Entered Medline: 19930205

AB High resolution **X-ray crystallography** has been used to determine the modes of binding to thermolysin of a series of different inhibitors including dipeptides, mercaptans, hydroxamates, N-carboxymethyl peptides and phosphonamidates. The interactions displayed by such inhibitors

illustrate interactions that are presumed to occur between the enzyme and its substrates during catalysis. The **crystallographic** analysis, together with model building, suggest a detailed stereochemical mechanism of action for thermolysin and, by analogy, other zinc proteases such as carboxypeptidase A and the **angiotensin converting enzyme.** Analysis of a series of phosphonamidates, which are presumed to be transition-state analogues, has shown that chemically similar inhibitors can adopt dissimilar modes of binding. These different configurations provide a rationalization for large differences in the kinetics of binding that are observed for these inhibitors. Experiments with thermolysin as a test case suggest that knowledge of the three-dimensional structure of an enzyme or receptor will greatly facilitate the rational design of drugs directed at such targets.

L44 ANSWER 55 OF 76 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 91140595 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1995891
TITLE: Configuration and preferential solid-state conformations of perindoprilat (S-9780). Comparison with the **crystal** structures of other ACE inhibitors and conclusions related to structure-activity relationships.
AUTHOR: Pascard C; Guilhem J; Vincent M; Remond G; Portevin B; Laubie M
CORPORATE SOURCE: Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France.
SOURCE: Journal of medicinal chemistry, (1991 Feb) 34 (2) 663-9. Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199103
ENTRY DATE: Entered STN: 19910412
Last Updated on STN: 19910412
Entered Medline: 19910327

AB The conformation of perindoprilat, an antihypertensive drug, is studied in the solid state by **X-ray** analysis. The resolution of its structure reveals important analogies between its observed conformation and that of several ACE inhibitors of the same family. This comparison points out a constant relative orientation of the functional groups, regardless of the molecular environment. This angular constancy appears to us as not being accidental and is a good argument for the spatial design of the ACE binding site. Although ACE is a carboxydipeptidase, the binding site may not contain two but one unique hydrophobic pocket receiving the C-terminal end of the inhibitors.

L44 ANSWER 56 OF 76 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 91140570 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1995872
TITLE: Molecular and **crystal** structures of MDL27,467A hydrochloride and quinapril hydrochloride, two ester derivatives of potent **angiotensin converting enzyme** inhibitors.

AUTHOR: Hausin R J; Codding P W
CORPORATE SOURCE: Department of Chemistry, University of Calgary, Alberta, Canada.
SOURCE: Journal of medicinal chemistry, (1991 Feb) 34 (2) 511-7.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199103
ENTRY DATE: Entered STN: 19910412
Last Updated on STN: 19910412
Entered Medline: 19910327

AB The molecular structures of MDL27,467A hydrochloride, [4 alpha,7 alpha(R*),12b beta]-7-[[1-(ethoxycarbonyl)-3-phenyl-propyl] amino]-1,2,3,4,6,7,12a,12b-octahydro-6-oxopyrido[2,1- a][2]benzazepine-4-carboxylic acid diphenylmethyl ester hydrochloride, and quinapril hydrochloride, [3S-[2[R*(R*)],3R]]-2-[2[[1- (ethoxycarbonyl)-3-phenylpropyl]-amino]-1-oxopropyl]-1,2,3,4- tetrahydro-3-isoquinolinecarboxylic acid hydrochloride, were determined by **X- ray** diffraction methods. The modified, C-terminal dipeptide portions and the phenylpropyl fragments in both **crystal** structures adopt similar conformations. The binding positions for several pharmacophores are defined by the constraint of the tricyclic system in the **crystallographic** structure of MDL27,467A hydrochloride. Conformational energy calculations show that the phenyl ring of the tetrahydro-3-isoquinoline system of quinapril does not fit into the S2 hydrophobic pocket of **angiotensin converting enzyme.**

L44 ANSWER 57 OF 76 MEDLINE on STN
ACCESSION NUMBER: 92040555 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1938102
TITLE: Structure and conformation of a novel inhibitor of angiotensin I converting enzyme--a tripeptide containing phosphonic acid.
AUTHOR: Hirayama N; Kasai M; Shirahata K
CORPORATE SOURCE: Tokyo Research Laboratories, Kyowa Hakko Kogyo Co. Ltd., Japan.
SOURCE: International journal of peptide and protein research, (1991 Jul) 38 (1) 20-4.
Journal code: 0330420. ISSN: 0367-8377.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199112
ENTRY DATE: Entered STN: 19920124
Last Updated on STN: 19920124
Entered Medline: 19911213

AB A novel phosphotripeptide, (IR)-1-(N-(N-acetyl-L-isoleucyl)-L-tyrosyl)amino-2-(4-hydroxyphenyl)ethy l- phosphonic acid, is a potent inhibitor of angiotensin I converting enzyme (ACE). ACE inhibitory activity in vitro of the peptide is comparable to that of captopril. Its diethylester (C29H42N3O8P, molecular weight, 591.6) **crystallizes** in the monoclinic space group C2, with cell constants: a = 25.666(9), b = 9.590(8), c = 13.557(2)A, beta = 91.65(2) degrees, Z = 4, Dc = 1.17

g/cm3. The structure was solved by MULTAN 11/82 and refined by full matrix least-squares methods to a final R-factor of 0.063 for 2123 unique reflections (F greater than 3 sigma(F) measured on an Enraf-Nonius CAD-4 diffractometer (CuK alpha, lambda = 1.541 8 A, T = 295 K). The absolute configuration of the alpha-carbon where the phosphonic acid is attached was determined unequivocally by referring to the L-isoleucyl moiety whose absolute configuration is known. The conformation of the molecule is relatively rigid owing to the intramolecular requisites and the resultant relative disposition of hetero atoms, which are necessary to its biological activities, are confined to the corresponding disposition in captopril.

L44 ANSWER 58 OF 76 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on
STN
ACCESSION NUMBER: 1991:605997 SCISEARCH Full-text
THE GENUINE ARTICLE: GM721
TITLE: INORGANIC-CHEMISTRY AND DRUG DESIGN
AUTHOR: SADLER P J (Reprint)
CORPORATE SOURCE: UNIV LONDON, BIRKBECK COLL, DEPT CHEM, LONDON WC1H 0PP, ENGLAND (Reprint)
COUNTRY OF AUTHOR: ENGLAND
SOURCE: ADVANCES IN INORGANIC CHEMISTRY, (1991) Vol. 36, pp. 1-48.
ISSN: 0065-2792.
PUBLISHER: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 150
ENTRY DATE: Entered STN: 1994
Last Updated on STN: 1994

L44 ANSWER 59 OF 76 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 90300488 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2362274
TITLE: **Crystallographic** studies of **angiotensin converting enzyme** inhibitors and analysis of preferred zinc coordination geometry.
AUTHOR: Hausin R J; Codding P W
CORPORATE SOURCE: Department of Chemistry, University of Calgary, Alberta, Canada.
SOURCE: Journal of medicinal chemistry, (1990 Jul) 33 (7) 1940-7.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199008
ENTRY DATE: Entered STN: 19900907
Last Updated on STN: 19970203
Entered Medline: 19900806
AB The molecular structures of two potent inhibitors of **angiotensin converting enzyme** (ACE, EC 3.4.15.1, dipeptidyl carboxypeptidase), ketoace, (5S)-5-benzamido-4-oxo-6-phenylhexanoyl-L- proline, and (1S,2R)-1-[[2-(benzoylthio)-cyclopentyl]carbonyl]-L-proline were

determined by **X-ray** diffraction methods. The distances between the binding functions in both **crystal** structures are in agreement with the experimental results for the hypertension drug captopril and the enzyme substrate hippuryl-L-histidyl-L- leucine. The modified peptide skeletons of both inhibitors adopt extended conformations with the proline amide bond trans. **Crystallographic** data have been used to determine the coordination geometry for zinc-sulfhydryl and zinc-carbonyl interactions. Coordination distances and bond angles are found to be different from values assumed in models of the **angiotensin converting enzyme** active site. No preferred torsion angles for a zinc-sulfhydryl inhibitor interaction can be identified. Superposition of the **crystallographic** structures of four ACE ligands shows that the observed extended conformations place the pharmacophores, zinc atom ligand, carbonyl oxygen atom, and carboxyl group, in juxtaposition and provide an alternative model for the interaction of ligands with the ACE active site.

L44 ANSWER 60 OF 76 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 88298426 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 3403371
TITLE: Structure elucidation of A58365A and A58365B, **angiotensin converting enzyme** inhibitors produced by Streptomyces chromofuscus.
AUTHOR: Hunt A H; Mynderse J S; Samlaska S K; Fukuda D S; Maciak G M; Kirst H A; Occolowitz J L; Swartzendruber J K; Jones N D
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285.
SOURCE: Journal of antibiotics, (1988 Jun) 41 (6) 771-9.
Journal code: 0151115. ISSN: 0021-8820.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198809
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19880915

AB A58365A and A58365B, **angiotensin converting enzyme** inhibitors isolated from the culture filtrate of Streptomyces chromofuscus NRRL 15098, are homologous compounds of molecular formulas C12H13NO6 and C13H15NO6. The molecular similarities of the two inhibitors were established by comparison of their 1H NMR, 13C NMR, and UV spectra. Catalytic hydrogenation of A58365A led to a tetrahydro-deoxy derivative, C12H17NO5; extensive 1H NMR decoupling studies at 360 MHz allowed all the non-exchangeable protons of the derivative to be connected in a continuous substructure. This fragment was combined with information from other spectroscopic methods to suggest the structures for A58365A (1) and A58365B (2); the conclusions were confirmed by an **X-ray crystallographic** analysis of A58365A-dimethyl ester.

L44 ANSWER 61 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1988:55878 CAPLUS Full-text
DOCUMENT NUMBER: 108:55878

TITLE: **Angiotensin-converting enzyme** inhibitors. 2. Perhydroazepin-2-one derivatives

AUTHOR(S): Yanagisawa, Hiroaki; Ishihara, Sadao; Ando, Akiko; Kanazaki, Takuro; Miyamoto, Shuichi; Koike, Hiroyuki; Iijima, Yasuteru; Oizumi, Kiyoshi; Matsushita, Yoichi; Hata, Tadashi

CORPORATE SOURCE: Chem. Res. Lab., Sankyo Co., Ltd., Tokyo, 140, Japan

SOURCE: Journal of Medicinal Chemistry (1988), 31(2), 422-8
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 108:55878

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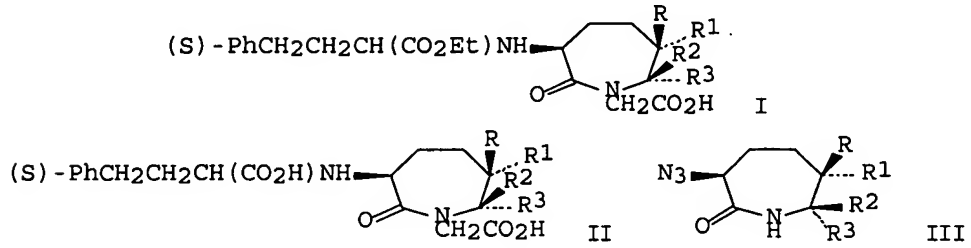

AB Chiral [[(carbethoxyphenylpropyl)amino]oxophenylperhydroazepino]acetic acids I (R = Ph, R1-R3 = H; R1 = Ph, R = R2 = R3 = H; R2 = Ph, R = R1 = R3 = H; R3 = Ph, R-R2 = H) and diacids II (same R-R3) were prepared and evaluated for **angiotensin-converting enzyme** inhibition. II (R or R1 or R2 = Ph) showed in vivo inhibition greater than that of enalaprilat. I (R or R1 or R2 = Ph), p.o. in rats, suppressed the pressor response to angiotensin I administered i.v. The structure-activity relationships of I and II were discussed based on MNDO calcns. of their conformations. The structures of azidoperhydroazepinones III (R = Ph, R1-R3 = H; R1 = Ph, R = R2 = R3 = H; R2 = Ph, R = R1 = R3 = H) were determined by **x-ray crystallog.**

L44 ANSWER 62 OF 76 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1988:370527 BIOSIS Full-text

DOCUMENT NUMBER: PREV198835055140; BR35:55140

TITLE: STRUCTURAL BASIS OF THE ACTION OF THERMOLYSIN AND THE ZINC PROTEASES.

AUTHOR(S): HOLDEN H M [Reprint author]; TRONRUD D E; RODERICK S; WEAVER L H; MATTHEWS B W

CORPORATE SOURCE: INST MOL BIOL, UNIV OREG, EUGENE, OREG 97403, USA

SOURCE: Journal of Cellular Biochemistry Supplement, (1988) No. 12

PART B, pp. 267.
Meeting Info.: SYMPOSIUM ON CELLULAR PROTEASES AND CONTROL
MECHANISMS HELD AT THE 17TH ANNUAL UCLA (UNIVERSITY OF CALIFORNIA-LOS ANGELES) MEETING ON MOLECULAR AND CELLULAR BIOLOGY, LAKE TAHOE, CALIFORNIA, USA, FEBRUARY 21-26, 1988.
J CELL BIOCHEM SUPPL.
ISSN: 0733-1959.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 9 Aug 1988
Last Updated on STN: 9 Aug 1988

L44 ANSWER 63 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 17
ACCESSION NUMBER: 1988:488769 CAPLUS Full-text
DOCUMENT NUMBER: 109:88769
TITLE: Molecular modeling of the active site of enkephalin-degrading neutral endopeptidase-24.11 (enkephalinase). An active site model for neutral endopeptidase-24.11
AUTHOR(S): Andrews, Peter R.; Iskander, Magdy N.; Issa, John; Reiss, James A.
CORPORATE SOURCE: Sch. Pharm. Chem., Victorian Coll. Pharm. Ltd., Parkville, 3052, Australia
SOURCE: Quantitative Structure-Activity Relationships (1988), 7(1), 1-6
CODEN: QSARDI; ISSN: 0722-3676
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The active site regions of thermolysin (TLN) and carboxypeptidase A (CPA) are directly compared by superimposition of the published **crystal** structures of 8 TLN-inhibitor complexes and 4 CPA-inhibitor complexes. There is a remarkable similarity in the S'1 region of these 2 Zn metalloenzymes, and it is suggested that this may be a common feature among other enzymes of this class, including the enkephalin-degrading neutral endopeptidase of enkephalinase (NEP-24.11). Assuming this common feature, the possible geometry of the S'2 region of enkephalinase was determined by performing classical potential energy calcns. on potent NEP-24.11 inhibitors. The active conformation of these inhibitors was thus identified as similar to that found in the **x-ray crystal** structure of TLN-inhibitor complexes. It is proposed that the active site region of TLN should serve as a reasonable model for that of NEP-24.11. Extension of the model to the case of **angiotensin - converting enzyme** (ACE) showed that this enzyme might have a similar S'1 region to the other 3 enzymes and allowed further definition of the ACE model previously developed.

L44 ANSWER 64 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1988:37803 CAPLUS Full-text
DOCUMENT NUMBER: 108:37803
TITLE: **Angiotensin-converting enzyme** inhibitors. Perhydro-1,4-thiazepin-5-one derivatives

AUTHOR(S): Yanagisawa, Hiroaki; Ishihara, Sadao; Ando, Akiko; Kanazaki, Takuro; Miyamoto, Shuichi; Koike, Hiroyuki; Iijima, Yasuteru; Oizumi, Kiyoshi; Matsushita, Yoichi; Hata, Tadashi

CORPORATE SOURCE: Chem. Res. Lab., Sankyo Co., Ltd., Tokyo, 140, Japan

SOURCE: Journal of Medicinal Chemistry (1987), 30(11), 1984-91

CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 108:37803

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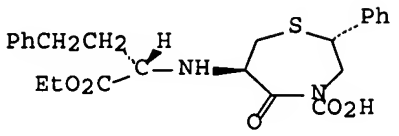

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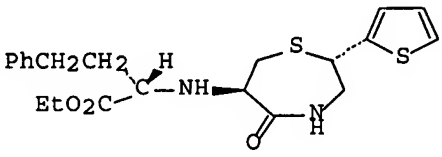

II

AB Aminooxoperhydrothiazepinylacetic acids, e.g. I, (monoester monoacids) and their dicarboxylic acids containing hydrophobic Ph or thienyl substituents at the 2- or 3-position of the thiazepinone ring were prepared and assayed for **angiotensin-converting enzyme** (ACE) inhibitory activity. The dicarboxylic acids having the pseudoequatorial amino groups at the 6-position and the pseudoequatorial hydrophobic substituents at the 2- or 3-position of the chair conformation of the thiazepinone ring had potent in vitro inhibitory activity. The monoester monoacids having the hydrophobic substituents at the 2-position suppressed pressor response to angiotensin I for a longer duration than those having the substituents at the 3-position when administered orally. The structure-activity relationship was studied by conformational energy calcns. of the thiazepinone ring. The **x-ray crystal** structure of 2-thienylperhydrothiazepinone II, an intermediate in the preparation of the N-carboxylated derivative, was determined

L44 ANSWER 65 OF 76 MEDLINE on STN DUPLICATE 18

ACCESSION NUMBER: 88011252 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 2821276

TITLE: Rat submaxillary gland serine protease, tonin. Structure solution and refinement at 1.8 A resolution.

AUTHOR: Fujinaga M; James M N

CORPORATE SOURCE: Department of Biochemistry, University of Alberta, Edmonton, Canada.

SOURCE: Journal of molecular biology, (1987 May 20) 195 (2) 373-96.

Journal code: 2985088R. ISSN: 0022-2836.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198711
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 20000303
Entered Medline: 19871113

AB Tonin is a mammalian serine protease that is capable of generating the vasoconstrictive agent, angiotensin II, directly from its precursor protein, angiotensinogen, a process that normally requires two enzymes, renin and **angiotensin-converting enzyme.** The **X-ray crystallographic** structure determination and refinement of tonin at 1.8 A resolution and the analysis of the resulting model are reported. The initial phases were obtained by the method of molecular replacement using as the search model the structure of bovine trypsin. The refined model of tonin consists of 227 amino acid residues out of the 235 in the complete molecule, 149 water molecules, and one zinc ion. The R-factor (R = sigma Fo - Fc/sigma Fo) is 0.196 for the 14,997 measured data between 8 and 1.8 A resolution with I greater than or equal to sigma (I). It is estimated that the overall root-mean-square error in the coordinates is about 0.3 A. The structure of tonin that has been determined is not in its active conformation, but one that has been perturbed by the binding of Zn2+ in the active site. Zn2+ was included in the buffer to aid the **crystallization.** Nevertheless, the structure of tonin that is described is for the most part similar to its native form as indicated by the close tertiary structural homology with kallikrein. The differences in the structures of the two enzymes are concentrated in several loop regions; these structural differences are probably responsible for the differences in their reactivities and specificities.

L44 ANSWER 66 OF 76 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 87229021 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 3295561
TITLE: High resolution **X-ray** analyses of renin inhibitor-aspartic proteinase complexes.
AUTHOR: Foundling S I; Cooper J; Watson F E; Cleasby A; Pearl L H;
Sibanda B L; Hemmings A; Wood S P; Blundell T L; Valler M J; +
SOURCE: Nature, (1987 May 28-Jun 3) 327 (6120) 349-52.
Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198707
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 20000303
Entered Medline: 19870702

AB Inhibitors of the conversion of angiotensinogen to the vasoconstrictor angiotensin II have considerable value as antihypertensive agents. For example, captopril and enalapril are clinically useful as inhibitors of **angiotensin-converting enzyme.** This has encouraged intense activity in the development of inhibitors of kidney renin, which is a very specific aspartic proteinase catalysing the first and rate limiting step in the conversion of angiotensinogen to angiotensin II. The most effective inhibitors such as H-142 and L-363,564 have used non-hydrolysable

analogues of the proposed transition state, and partial sequences of angiotensinogen (Table 1). H-142 is effective in lowering blood pressure in humans but has no significant effect on other aspartic proteinases such as pepsin in the human body (Table 1). At present there are no **crystal** structures available for human or mouse renins although three-dimensional models demonstrate close structural similarity to other spartic proteinases. We have therefore determined by **X -ray** analysis the three-dimensional structures of H-142 and L-363,564 complexed with the aspartic proteinase endothiapepsin, which binds these inhibitors with affinities not greatly different from those measured against human renin (Table 1). The structures of these complexes and of that between endothiapepsin and the general aspartic proteinase inhibitor, H-256 (Table 1) define the common hydrogen bonding schemes that allow subtle differences in side-chain orientations and in the positions of the transition state analogues with respect to the active-site aspartates.

L44 ANSWER 67 OF 76 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1988:434641 BIOSIS Full-text
DOCUMENT NUMBER: PREV198835086771; BR35:86771
TITLE: **CRYSTALLOGRAPHIC** STUDIES OF REDUCED BOND INHIBITORS COMPLEXED WITH AN ASPARTIC PROTEINASE.
AUTHOR(S): FOUNDLING S I [Reprint author]; COOPER J; WATSON F E; PEARL L H; HEMMINGS A; WOOD S P; BLUNDELL T; HALLETT A; JONES D M; ET AL
CORPORATE SOURCE: LAB MOLECULAR BIOL, DEP CRYSTALLOGRAPHY, BIRBECK COLL, MALET ST, LONDON WC1E 7HX, UK
SOURCE: Journal of Cardiovascular Pharmacology, (1987) Vol. 10, No. SUPPL. 7, pp. S59-S68.
Meeting Info.: SATELLITE SYMPOSIUM ON INHIBITORS OF THE RENIN-ANGIOTENSIN SYSTEM TO THE 11TH INTERNATIONAL SOCIETY OF HYPERTENSION, HEIDELBERG, WEST GERMANY, SEPTEMBER 5, 1986. J CARDIOVASC PHARMACOL.
CODEN: JCPCDT. ISSN: 0160-2446.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 24 Sep 1988
Last Updated on STN: 24 Sep 1988

L44 ANSWER 68 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 20

ACCESSION NUMBER: 1986:552979 CAPLUS Full-text
DOCUMENT NUMBER: 105:152979
TITLE: Conformational similarities of **angiotensin-converting enzyme** inhibitors: **x-ray crystal** structures
AUTHOR(S): In, Yasuko; Shibata, Megumi; Doi, Mitsunobu; Ishida, Toshimasa; Inoue, Masatoshi; Sasaki, Yasuto; Morimoto, Shiro
CORPORATE SOURCE: Osaka Coll. Pharm., Osaka, 580, Japan
SOURCE: Journal of the Chemical Society, Chemical

Communications (1986), (6), 473-4
CODEN: JCCCAT; ISSN: 0022-4936
DOCUMENT TYPE: Journal
LANGUAGE: English
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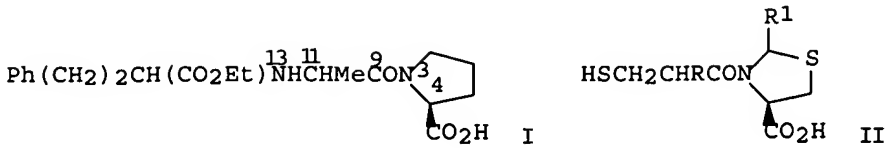
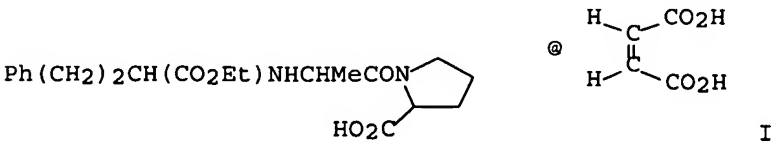


I II

AB The structures of enalapril (MK 421) (I) and the thio analogs YS 980 (II; R = Me, R1 = H) and SA 446 (II; R = H, R1 = 2-HOC6H4), potent **angiotensin-converting enzyme** inhibitors, were determined by **x-ray crystallog.** anal. All 3 possess a common conformation with a trans zigzag geometry of the C(4)-N(3)-C(9)-C(11)-C(13)[N(13)] bond sequence and a cis orientation between the carboxy and amido carbonyl groups.

L44 ANSWER 69 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1986:193011 CAPLUS Full-text
DOCUMENT NUMBER: 104:193011
TITLE: High resolution spectroscopic evidence and solution calorimetry studies on the polymorphs of enalapril maleate
AUTHOR(S): Ip, Dominic P.; Brenner, Gerald S.; Stevenson, James M.; Lindenbaum, Siegfried; Douglas, Alan W.; Klein, S.
David; McCauley, James A.
CORPORATE SOURCE: Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: International Journal of Pharmaceutics (1986), 28(2-3), 183-91
CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Enalapril maleate (I) [76095-16-4], a potent **angiotensin- converting enzyme** inhibitor, exists as polymorphs form I and form II. **X-ray** powder diffraction measurements have shown slightly different patterns. Differential scanning calorimetric thermograms failed to show any significant differences during melting. High resolution spectroscopic techniques, including solid state C-13 NMR, Fourier-transform IR and Raman, detect differences between form I and form II. Heats of solution data obtained also indicate measurable energy differences. Apparently, these 3 polymorphic forms of I are energetically very similar. Virtual equivalence of in vitro dissoln. rate was obtained from formulations of I made from either form I, or form II, or mixts.

L44 ANSWER 70 OF 76 MEDLINE on STN

ACCESSION NUMBER:	85303482 MEDLINE Full-text
DOCUMENT NUMBER:	PubMed ID: 2994404
TITLE:	The design and properties of N-carboxyalkyldipeptide inhibitors of **angiotensin-converting enzyme.**
AUTHOR:	Patchett A A; Cordes E H
SOURCE:	Advances in enzymology and related areas of molecular biology, (1985) 57 1-84. Ref: 188 Journal code: 0337243. ISSN: 0065-258X.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	198510
ENTRY DATE:	Entered STN: 19900320 Last Updated on STN: 20000303 Entered Medline: 19851010

AB **Angiotensin-converting enzyme** inhibitors promise to make important therapeutic contributions to the control of hypertension and congestive heart failure. The nonapeptide teprotide was the first of these inhibitors to be tested clinically. It was followed by orally active inhibitors, captopril in 1977 and enalapril in 1980. The latter is representative of a new design for the inhibition of metallopeptidases and is the subject of this review. The best of the N-carboxyalkyldipeptide inhibitors inhibits **angiotensin- converting enzyme** with a Ki of 7.6 X 10(-11) M. This compound is the most potent competitive inhibitor of a metallopeptidase yet to have been reported. The basis of this high potency is beginning to be understood and in part is considered to involve precisely arranged multiple interactions within the enzyme active site. **X- ray crystallography** of a thermolysin-inhibitor complex has been achieved. Assuming that similar interactions within the active site of **angiotensin-converting enzyme** are mechanistically probable, the authors hypothesize the binding of enalaprilat to converting enzyme as shown in Figure 24. Such interactions are consistent with kinetic studies (Section V) with the understanding that binding to the enzyme is not sensitive to the inhibitor's state of NH protonation. The reason for this surprising conclusion has not been established. Perhaps counterbalancing factors are involved in the energetics of binding or there may be compensating adjustments made in the enzyme which permit NH protonated and nonprotonated inhibitor to bind equally well. Figure 24 also summarizes present understanding of the conformation of enalaprilat when bound to

angiotensin- converting enzyme. From studies on conformationally defined analogs of enalaprilat, it seems likely that the Ala-Pro segment of enalaprilat binds in a conformation that is close to a minimum energy conformer. This situation no doubt contributes to the potency of enalaprilat, since little binding energy would be needed to induce conformational changes in this part-structure of enalaprilat when it is bound to the enzyme. The phenethyl group of enalaprilat is believed to be near the alpha-hydrogen of the L-Ala residue in the enzyme-inhibitor complex. However, the synthesis of conformationally restricted analogs to establish this point has not yet been reached. The N-carboxyalkylpeptide design was developed from Wolfenden's collected product inhibitors of carboxypeptidase-A. Whether or not N-carboxyalkyldipeptides should be classified as collected product or transition state inhibitors is unclear.(ABSTRACT TRUNCATED AT 400 WORDS)

L44 ANSWER 71 OF 76 MEDLINE on STN DUPLICATE 21
ACCESSION NUMBER: 84280080 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 6087816
TITLE: Azapeptides: a new class of **angiotensin-converting enzyme** inhibitors.
AUTHOR: Greenlee W J; Thorsett E D; Springer J P; Patchett A A; Ulm E H; Vassil T C
SOURCE: Biochemical and biophysical research communications, (1984 Jul 31) 122 (2) 791-7.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198409
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19840912

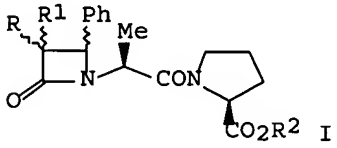
AB A class of potent inhibitors of **angiotensin-converting enzyme** (dipeptidyl carboxypeptidase, E.C. 3.4.15.1) is reported, in which an alpha-aza substitution into the substituted N-carboxymethyl dipeptide structure of enalapril is made. The inhibitors 2 exhibit striking alterations in their conformational and acid-base properties due to the aza substitution, as is clear from pKa data and the **x- ray crystal** structure of a model azapeptide. In spite of this, they bind tightly to the enzyme, with inhibitor potency comparable to that of captopril.

L44 ANSWER 72 OF 76 MEDLINE on STN DUPLICATE 22
ACCESSION NUMBER: 85174894 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 6085275
TITLE: The chemistry of enalapril.
AUTHOR: Patchett A A
SOURCE: British journal of clinical pharmacology, (1984) 18 Suppl 2 201S-207S. Ref: 19
Journal code: 7503323. ISSN: 0306-5251.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

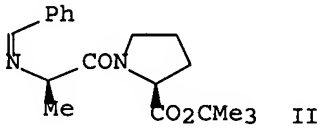
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198506
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850611

AB The design origins of the potent non-mercapto **angiotensin converting enzyme** inhibitors enalaprilat and its mono ethyl ester enalapril are described. Lactam analogues of enalaprilat have provided some insight into the conformation of this inhibitor when it is bound to converting enzyme. **X-ray crystallographic** studies of a related enzyme/inhibitor complex offer an explanation for the high potency and specificity of these and related inhibitors.

L44 ANSWER 73 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 23
ACCESSION NUMBER: 1984:192245 CAPLUS Full-text
DOCUMENT NUMBER: 100:192245
TITLE: The synthesis of peptide β-lactams as potential protease inhibitors
AUTHOR(S): Wharton, Clifford J.; Wrigglesworth, Roger; Rowe, Michael
CORPORATE SOURCE: Dep. Med. Chem., Wellcome Res. Lab., Beckenham, BR3 3BS, UK
SOURCE: Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1984), (1), 29-39
CODEN: JCPRB4; ISSN: 0300-922X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



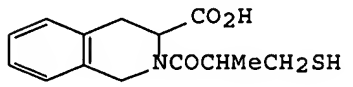
II

AB Mixts. of cis peptide β-lactams I (R = PhO, PhCH2O, HO, Cl, Br, R1 = H; R = PhSe, R1 = Me; R2 = CMe3, H) were prepared through cycloaddn. of imine II with RCHR1COCl. I are as potential inhibitors of **angiotensin-converting enzyme.** The absolute configurations of I were determined by NMR studies including nuclear Overhauser effect studies, and by **x-ray crystallog.** anal. of I (R = β-PhO, R1 = α-H, R2 = CMe3; α-Ph).

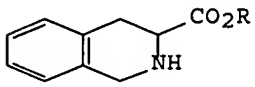
L44 ANSWER 74 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 24
ACCESSION NUMBER: 1983:522249 CAPLUS Full-text
DOCUMENT NUMBER: 99:122249
TITLE: Studies on **angiotensin-converting**

	enzyme inhibitors. I. Syntheses and **angiotensin-converting enzyme** inhibitory activity of 2-(3-mercaptopropionyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives
AUTHOR(S):	Hayashi, Kimiaki; Ozaki, Yasuhiko; Nunami, Kenichi; Uchida, Tomofumi; Kato, Jyoji; Kinashi, Keizo; Yoneda, Naoto
CORPORATE SOURCE:	Res. Lab. Appl. Biochem., Tanabe Seiyaku Co., Ltd., Osaka, 532, Japan
SOURCE:	Chemical & Pharmaceutical Bulletin (1983), 31(2), 570-6 CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE:	Journal
LANGUAGE:	English

GI



I



II

AB (3S)-2-[(2S)-3-Mercapto-2-methylpropionyl]-1,2,3,4-tetrahydroisoquinoline- 3-carboxylic acid (I) was prepared by the reaction of (3S)-II (R = CMe3, CH2Ph) with ClCOCHMeCH2SBz, followed by fractional **crystallization** and removal of the protective group. The absolute configuration of I was confirmed by **x-ray** diffraction anal. of the thiazepino[4,3-b]isoquinoline derived from I by cyclization. Resolution of HO2CCHMeCH2SBz was completed by using optically active phenylalanine amide as the resolving agent. The other optical isomers of I were prepared by treating (3S)- or (3R)-II (R = CH2Ph) with optically active ClCOCHMeCH2SBz. I was the most potent inhibitor of **angiotensin- converting enzyme** (III) in vitro with an ED50 of 8.6 + 10-9 M. I induced a dose-dependent inhibition of the pressor response to angiotensin I after oral administration to normotensive anesthetized rats. Moreover, I markedly reduced the systolic blood pressure in renal hypertensive rats and spontaneously hypertensive rats. The in vivo III inhibitory activity and the hypotensive effects of I were comparable to those of captopril.

L44 ANSWER 75 OF 76 MEDLINE on STN DUPLICATE 25

ACCESSION NUMBER:	83125670 MEDLINE Full-text
DOCUMENT NUMBER:	PubMed ID: 6297413
TITLE:	Widespread foreign-body granulomas and elevated serum **angiotensin-converting enzyme.**
AUTHOR:	Pucevich M V; Rosenberg E W; Bale G F; Terzakis J A
SOURCE:	Archives of dermatology, (1983 Mar) 119 (3) 229-34. Journal code: 0372433. ISSN: 0003-987X.
PUB. COUNTRY:	United States

DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198303
ENTRY DATE: Entered STN: 19900318
Last Updated on STN: 19900318
Entered Medline: 19830324

AB A patient had extensive foreign-body granulomatous inflammation of multiple skin sites and of the inguinal lymph nodes with splenomegaly, cutaneous anergy to common skin antigens, and peripheral blood eosinophilia. The patient had an elevated serum **angiotensin- converting enzyme** level. Histologically, the granulomas were of the foreign-body type with lymphocytes, histiocytes, eosinophils, and giant cells, some that contained doubly refractile **crystalline** material. Electron-probe **x-ray** microanalysis identified silicon, magnesium, iron, calcium, phosphorus, zinc, titanium, and chromium in the **crystalline** material. These findings suggest talc, cement, and inorganic pigment as possible sources of the **crystals.** This case is reported for its unusual clinical, laboratory, and morphologic features.

L44 ANSWER 76 OF 76 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1980:124092 CAPLUS Full-text
DOCUMENT NUMBER: 92:124092
TITLE: Characterization of the active site of **angiotensin converting enzyme**
AUTHOR(S): Buenning, P.; Holmquist, B.; Riordan, J. F.
CORPORATE SOURCE: Harvard Med. Sch., Peter Bent Brigham Hosp., Boston, MA, 02115, USA
SOURCE: Colloquium der Gesellschaft fuer Biologische Chemie (1979), 30(Biol. Funct. Proteinases), 269-75
CODEN: CGBCA9; ISSN: 0366-5887
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The compns. of the active sites and the catalytic mechanisms of carboxypeptidase A (I) and thermolysin have been previously investigated in depth by studies with chelating agents and chemical modification reagents as well as by **x-ray crystallog.** The similarities between the active sites of these 2 Zn-containing proteases and the active site of **angiotensin-converting enzyme** (II) enabled an initial working hypothesis for the catalytic mechanism of II to be suggested. By analogy to I, the same overall scheme for II was proposed. In both enzymes, the substrate interacts through its carbonyl group with the active site Zn atom to facilitate a general base or nucleophilic attack of the carboxyl group that leads to hydrolysis. Tyrosine donates a proton to the scissile peptide NH group, while specificity is determined by interaction of the terminal carboxyl group with an arginine and the hydrophobic R group with a hydrophobic pocket. One difference is found, however. Probably a critical lysyl residue also participates in the function of II and is possibly related to the requirements of monovalent anions, notably chloride, for enzymic activity. An essential lysyl residue is apparently not present in I. Nevertheless, it appears that a similar mechanistic process has evolved for both carboxypeptidases. Furthermore, a close relation between the active sites of I and thermolysin has been verified by **x- ray crystallog.**, and they likely

represent the products of convergent evolution. Apparently, these 3 Zn-containing proteases, while differing in specificities, have similar active sites. In fact, it may well be that all of the Zn-containing exo- and endoproteases share a common catalytic mechanism, much the same as the serine proteases share the well-known carboxylate-histidyl-serine triad.

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☐	L3	angiotensin-converting enzyme and crystal and x-ray	125
☐	L2	L1	0
	DB=PGPB; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
☐	L1	angiotensin-converting enzyme and crystal and x-ray	121

END OF SEARCH HISTORY

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1UZF

Title COMPLEX OF THE ANTI-HYPERTENSIVE DRUG CAPTOPRIL AN THE HUMAN TESTICULAR ANGIOTENSIN I-CONVERTING ENZYME

Authors Natesh, R., Schwager, S.L.U., Evans, H.R., Sturrock, E.D., Acharya, K.R.

Primary Citation **Natesh, R., Schwager, S.L.U., Evans, H.R., Sturrock, E.D., Acharya, K.R.** Structural Details on the Binding of Antihypertensive Drugs Captopril and Enalaprilat to Human Testicular Angiotensin I-Converting Enzyme *Biochemistry v43 pp.8718 , 2004*

History Deposition 2004-03-11 Release 2004-07-16

Experimental Method Type X-RAY DIFFRACTION Data N/A

Parameters

Resolution[Å]	R-Value	R-Free	Space Group
2.00	0.184 (obs.)	0.227	P 2_1 2_1 2_1

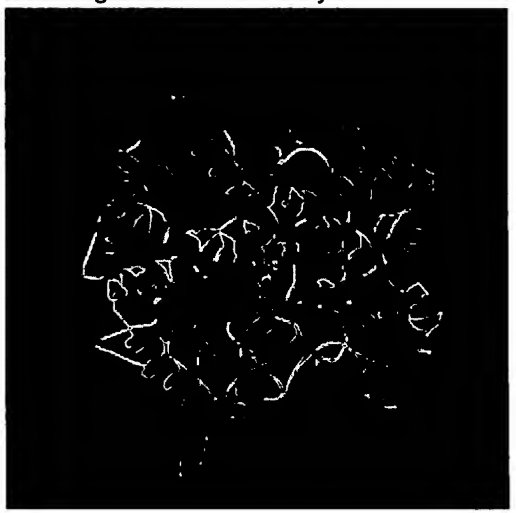
Unit Cell

Length [Å]	a	56.65	b	84.90	c	133.50
Angles [°]	alpha	90.00	beta	90.00	gamma	90.00

Molecular Description Polymer: 1 Molecule: ANGIOTENSIN CONVERTING ENZYME Fragment: EXTRACELLULAR DOMAIN, RESIDUES 68-656 Chains: A;

Images and Visualization

Biological Molecule / Asymmetric Unit



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Functional Class **Metalloprotease**

Source Polymer: 1 Scientific Name: Homo sapiens Common Name: Human Expression system: Chinese hamster ovary

Chemical Component

Identifier	Name	Formula	Drug Similarity	Ligand Structure	Ligand Interaction
ZN	ZINC ION	Zn^{2+}	[View]	[View]	[View]
NAG	N-ACETYL-D-GLUCOSAMINE	$C_8H_{15}NO_6$	[View]	[View]	[View]
MCO	1-(3-MERCAPTO-2-METHYL-PROPIONYL)-PYRROLIDINE-2-CARBOXYLIC ACID	$C_9H_{15}NO_3S$	[View]	[View]	[View]
CL	CHLORIDE ION	Cl^-	[View]	[View]	[View]

SCOP Classification (version 1.69)

Domain Info	Class	Fold	Superfamily	Family	Domain	Species
d1uzfa_	Alpha and beta proteins (a+b)	Zincin-like	Metalloproteases ("zincins"), catalytic domain	Neurolysin-like	Angiotensin converting enzyme, ACE	Human (Homo sapiens)

CATH Classification (version v2.6.0)

Domain	Class	Architecture	Topology	Homology
1uzfA2	Mainly Alpha	Orthogonal Bundle	Neurolysin; domain 3	Neurolysin, domain 3

GO Terms

Polymer	Molecular Function	Biological Process	Cellular Component
ANGIOTENSIN CONVERTING ENZYME (1UZF:A)	• peptidyl-dipeptidase A activity • metallopeptidase activity • zinc ion binding	• proteolysis	• membrane

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1O86

Title	CRYSTAL STRUCTURE OF HUMAN ANGIOTENSIN CONVERING ENZYME IN COMPLEX WITH LISINOPRIL.
Authors	Natesh, R., Schwager, S.L.U., Sturrock, E.D., Acharya, K.R.
Primary Citation	**Natesh, R., Schwager, S., Sturrock, E., Acharya, K.** Crystal Structure of the Human Angiotensin-Converting Enzyme-Lisinopril Complex *Nature v421 pp.551 , 2003*
History	Deposition 2002-11-25 Release 2003-02-07
Experimental Method	Type X-RAY DIFFRACTION Data N/A

Parameters

Resolution[Å]	R-Value	R-Free	Space Group
2.00	0.180 (obs.)	0.220	P 2_1 2_1 2_1

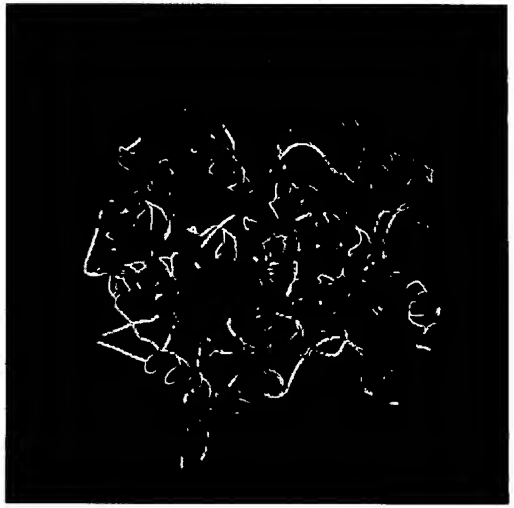
Unit Cell

Length [Å]	a	56.47	b	84.90	c	133.99
Angles [°]	alpha	90.00	beta	90.00	gamma	90.00

Molecular Description	Polymer: 1 Molecule: ANGIOTENSIN CONVERTING ENZYME Fragment: RESIDUES 68-656 Chains: A; EC No.: 3.4.15.1 (EC)
Functional Class	**Metalloprotease**

Images and Visualization

Biological Molecule / Asymmetric Unit



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Source

Polymer: 1 Scientific Name: Homo sapiens Common Name: Human Expression system: Chinese hamster ovary cell

Chemical Component

Identifier	Name	Formula	Drug Similarity	Ligand Structure	Ligand Interaction
ZN	ZINC ION	Zn^{2+}	[View]	[View]	[View]
LPR	[N2-[(S)-1-CARBOXY-3-PHENYLPROPYL]-L-LYSYL- L-PROLINE	$C_{21}H_{31}N_3O_5$	[View]	[View]	[View]
CL	CHLORIDE ION	Cl^-	[View]	[View]	[View]

SCOP Classification (version 1.69)

Domain Info	Class	Fold	Superfamily	Family	Domain	Species
d1o86a_	Alpha and beta proteins (a+b)	Zincin-like	Metalloproteases ("zincins"), catalytic domain	Neurolysin-like	Angiotensin converting enzyme, ACE	Human (Homo sapiens)

CATH Classification (version v2.6.0)

Domain	Class	Architecture	Topology	Homology
1o86A2	Mainly Alpha	Orthogonal Bundle	Neurolysin; domain 3	Neurolysin, domain 3

GO Terms

Polymer	Molecular Function	Biological Process	Cellular Component
ANGIOTENSIN CONVERTING ENZYME (1O86:A)	• peptidyl-dipeptidase A activity • metallopeptidase activity • zinc ion binding	• proteolysis	• membrane

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1R4L

Title Inhibitor Bound Human Angiotensin Converting Enzyme-Related Carboxypeptidase (ACE2)

Authors Towler, P., Staker, B., Prasad, S.G., Menon, S., Ryan, D., Tang, J., Parsons, T., Fisher, M., Williams, D., Dales, N.A., Patane, M.A., Pantoliano, M.W.

Primary Citation **Towler, P., Staker, B., Prasad, S.G., Menon, S., Tang, J., Parsons, T., Ryan, D., Fisher, M., Williams, D., Dales, N.A., Patane, M.A., Pantoliano, M.W.** ACE2 X-Ray Structures Reveal a Large Hinge-bending Motion Important for Inhibitor Binding and Catalysis *J.Biol.Chem. v279 pp.17996-18007 , 2004*

History Deposition 2003-10-07 Release 2004-02-03

Experimental Method Type X-RAY DIFFRACTION Data [EDS]

Parameters

Resolution[Å]	R-Value	R-Free	Space Group
3.00	0.253 (work)	0.337	C 2 (C 1 2 1)

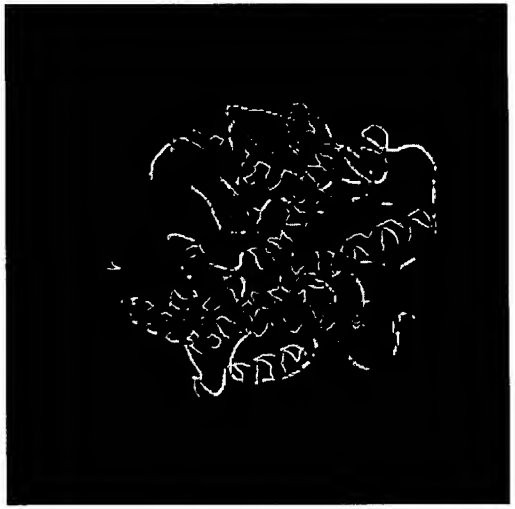
Unit Cell

Length [Å]	a	100.53	b	86.51	c	105.86
Angles [°]	alpha	90.00	beta	103.65	gamma	90.00

Molecular Description Polymer: 1 Molecule: angiotensin I converting enzyme 2 Fragment: Extracellular domains Chains: A; Polymer: 2 Molecule: disordered segment of collectrin homology domain Chains: B; Polymer: 3 Molecule:

Images and Visualization

Biological Molecule / Asymmetric Unit



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disordered segment of collectrin homology domain Chains: C; Polymer: 4 Molecule: disordered segment of collectrin homology domain Chains: D; Polymer: 5 Molecule: disordered segment of collectrin homology domain Chains: E;

Functional Class **Hydrolase**

Source Polymer: 1 Scientific Name: Homo sapiens Common Name: Human Expression system: Spodoptera frugiperda Polymer: 2 Scientific Name: Homo sapiens Common Name: Human Expression system: Spodoptera frugiperda Polymer: 3 Scientific Name: Homo sapiens Common Name: Human Expression system: Spodoptera frugiperda Polymer: 4 Scientific Name: Homo sapiens Common Name: Human Expression system: Spodoptera frugiperda Polymer: 5 Scientific Name: Homo sapiens Common Name: Human Expression system: Spodoptera frugiperda

Related PDB Entries

Id	Details
1R42	Native Human Angiotensin Converting Enzyme-Related Carboxypeptidase (ACE2)

Chemical Component

Identifier	Name	Formula	Drug Similarity	Ligand Structure	Ligand Interaction
ZN	ZINC ION	Zn^{2+}	[View]	[View]	[View]
XX5	(S,S)-2-{1-CARBOXY-2-[3-(3,5-DICHLORO-BENZYL)- 3H-IMIDAZOL-4-YL]-ETHYLAMINO}-4-METHYL-PENTANOIC ACID	$C_{19}H_{22}N_3O_4Cl_2$	[View]	[View]	[View]
UNK	UNKNOWN	Unknown	[View]	[View]	[View]
NAG	N-ACETYL-D-GLUCOSAMINE	$C_8H_{15}NO_8$	[View]	[View]	[View]
CL	CHLORIDE ION	Cl^-	[View]	[View]	[View]

SCOP Classification (version 1.69)

Domain Info	Class	Fold	Superfamily	Family	Domain	Species
d1r4la_	Alpha and beta proteins (a+b)	Zincin-like	Metalloproteases ("zincins"), catalytic domain	Neurolysin-like	Angiotensin converting enzyme 2, ACE2	Human (Homo sapiens)

GO Terms	Polymer	Molecular Function	Biological Process	Cellular Component
	angiotensin I converting enzyme 2 (1R4L:A)	• peptidyl-dipeptidase A activity • metallopeptidase activity • zinc ion binding	• proteolysis	• membrane
	disordered segment of collectrin homology domain (1R4L:B)	• none	• none	• none
	disordered segment of collectrin homology domain (1R4L:C)	• none	• none	• none
	disordered segment of collectrin homology domain (1R4L:D)	• none	• none	• none
	disordered segment of collectrin homology domain (1R4L:E)	• none	• none	• none

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1R42

Title Native Human Angiotensin Converting Enzyme-Related Carboxypeptidase (ACE2)

Authors Towler, P., Staker, B., Prasad, S.G., Menon, S., Ryan, D., Tang, J., Parsons, T., Fisher, M., Williams, D., Dales, N.A., Patane, M.A., Pantoliano, M.W.

Primary Citation **Towler, P., Staker, B., Prasad, S.G., Menon, S., Tang, J., Parsons, T., Ryan, D., Fisher, M., Williams, D., Dales, N.A., Patane, M.A., Pantoliano, M.W.** ACE2 X-Ray Structures Reveal a Large Hinge-bending Motion Important for Inhibitor Binding and Catalysis *J.Biol.Chem. v279 pp.17996-18007 , 2004*

History Deposition 2003-10-07 Release 2004-02-03

Experimental Method Type X-RAY DIFFRACTION Data [EDS]

Parameters

Resolution[Å]	R-Value	R-Free	Space Group
2.20	0.235 (work)	0.287	C 2 (C 1 2 1)

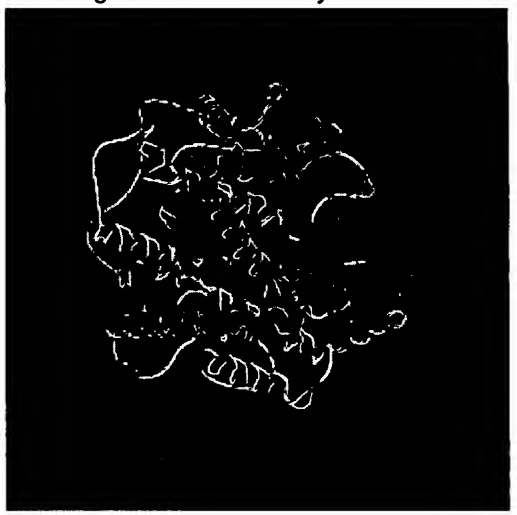
Unit Cell

Length [Å]	a	103.64	b	89.48	c	112.40
Angles [°]	alpha	90.00	beta	109.15	gamma	90.00

Molecular Description Polymer: 1 Molecule: angiotensin I converting enzyme 2 Fragment: Extracellular domains Chains: A; Polymer: 2 Molecule: disordered segment of collectrin homology domain Chains: B; Polymer: 3 Molecule:

Images and Visualization

Biological Molecule / Asymmetric Unit



Display Options

KiNG
Jmol
WebMol
Protein Workshop
QuickPDB
All Images

disordered segment of collectrin homology domain Chains: C; Polymer: 4 Molecule: disordered segment of collectrin homology domain Chains: D; Polymer: 5 Molecule: disordered segment of collectrin homology domain Chains: E;

Functional Class **Hydrolase**

Source Polymer: 1 Scientific Name: Homo sapiens Common Name: Human Expression system: Spodoptera frugiperda Polymer: 2 Scientific Name: Homo sapiens Common Name: Human Expression system: Spodoptera frugiperda Polymer: 3 Scientific Name: Homo sapiens Common Name: Human Expression system: Spodoptera frugiperda Polymer: 4 Scientific Name: Homo sapiens Common Name: Human Expression system: Spodoptera frugiperda Polymer: 5 Scientific Name: Homo sapiens Common Name: Human Expression system: Spodoptera frugiperda

Related PDB Entries

Id	Details
1R4L	Inhibitor bound Human Angiotensin Converting Enzyme-Related Carboxypeptidase (ACE2)

Chemical Component

Identifier	Name	Formula	Drug Similarity	Ligand Structure	Ligand Interaction
ZN	ZINC ION	Zn^{2+}	[View]	[View]	[View]
UNK	UNKNOWN	Unknown	[View]	[View]	[View]
NAG	N-ACETYL-D-GLUCOSAMINE	$C_8H_{15}NO_6$	[View]	[View]	[View]
CL	CHLORIDE ION	Cl^-	[View]	[View]	[View]

SCOP Classification (version 1.69)

Domain Info	Class	Fold	Superfamily	Family	Domain	Species
d1r42a_	Alpha and beta proteins (a+b)	Zincin-like	Metalloproteases ("zincins"), catalytic domain	Neurolysin-like	Angiotensin converting enzyme 2, ACE2	Human (Homo sapiens)

GO Terms

Polymer	Molecular Function	Biological Process	Cellular Component
	• peptidyl-dipeptidase A		

angiotensin I converting enzyme 2 (1R42:A)	• metallopeptidase activity • zinc ion binding	• proteolysis	• membrane
disordered segment of collectrin homology domain (1R42:B)	• none	• none	• none
disordered segment of collectrin homology domain (1R42:C)	• none	• none	• none
disordered segment of collectrin homology domain (1R42:D)	• none	• none	• none
disordered segment of collectrin homology domain (1R42:E)	• none	• none	• none

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